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"Unknown","Unknown","Unknown","Unknown","","","1998","","Legislative roundup: protection of human subjects key issue for Congress","Journal of the National Cancer Institute","90(2):97-8","f6739963-6ceb-4d01-ae33-6e72618ba3d1","","","RefMan","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2009","","CROI round-up. New information on the heart, plus a possible alternative to Norvir and more","Positively aware : the monthly journal of the Test Positive Aware Network","20(3):30-1","fd7be3b1-bab1-4d3a-8dd9-ba807b03f266","","","RefMan","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2012","","Preface","Adv. Mol. Toxicol.","6:xi-xii","4f7cele5-b6ce-44bf-9c74-5d0c452d3a23","","","RefMan","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2014","","Technology focus drives biologics development","Sp2","34-35","fa2e1849-d8c1-4f05-a91a-b2200e2374a1","","This article provides a roundup of recent developments in the biologics sector, highlighting how new technologies are driving its success through the discovery and development of new treatments to serve unmet medical needs."","","RefMan","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2015","","Glyphosate","IARC Monogr. Eval. Carcinog. Risks Hum.","112","8ae7d900-3bb0-4cb4-a19b-83add0d24760","","","RefMan","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2015","","Public health round-up","","93(1):5-6","a8c21ce7-af21-47c6-b39a-52144b8d821b","","","RefMan","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","1999","Acquavella, J., Farmer, D., Cullen, M. R.","A case-control study of non-Hodgkin lymphoma and exposure to pesticides","Cancer","86(4):729-31","5fffe00b-61d4-44f9-a8b8-897f247f7518","","","RefMan","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2007","Akaza, H.","Report from the 1st Japanese Urological Association-Japanese Society of Medical Oncology joint conference, 2006: 'A step towards better collaboration between urologists and medical oncologists',"International journal of urology : official journal of the Japanese Urological Association","14(5):375-83","d82586fd-9d9c-48ce-9bab-3829195517b2","","The 1st Japanese Urological Association-Japanese Society of Medical Oncology Joint Conference, titled 'A step towards better collaboration between urologists and medical oncologists', was held to coincide with the 44th Meeting of the Japan Society of Clinical Oncology, Tokyo, in October 2006. The main theme of the conference addressed the need for a subspecialty of medical oncologist within urology to keep abreast of advances in medical oncology. Urologists should become more involved in the postoperative management of urologic cancer. Consensus on the optimal way to move forward in the treatment of urological cancer is needed. The conference featured eight lectures surveying the present status of uro-oncology in Europe, the USA, Korea, Singapore, and Japan; the relationship between surgical oncologists and medical oncologists; global trends and international clinical trials in uro-oncology; and the

future of urologic oncology. These were followed by a general discussion titled 'Achieving better collaboration between the surgical oncologist and the medical oncologist.' This report presents a roundup of the 1st Japanese Urological Association-Japanese Society of Medical Oncology Joint Conference.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2013", "Alavanja, M. C. R., Ross, M. K., Bonner, M. R.", "Increased cancer burden among pesticide applicators and others due to pesticide exposure", "", "63(2):120-142", "81319346-9ba4-48b8-8358-e01f10eale0c", "", "A growing number of well-designed epidemiological and molecular studies provide substantial evidence that the pesticides used in agricultural, commercial, and home and garden applications are associated with excess cancer risk. This risk is associated both with those applying the pesticide and, under some conditions, those who are simply bystanders to the application. In this article, the epidemiological, molecular biology, and toxicological evidence emerging from recent literature assessing the link between specific pesticides and several cancers including prostate cancer, non-Hodgkin lymphoma, leukemia, multiple myeloma, and breast cancer are integrated. Although the review is not exhaustive in its scope or depth, the literature does strongly suggest that the public health problem is real. If we are to avoid the introduction of harmful chemicals into the environment in the future, the integrated efforts of molecular biology, pesticide toxicology, and epidemiology are needed to help identify the human carcinogens and thereby improve our understanding of human carcinogenicity and reduce cancer risk. © 2013 American Cancer Society, Inc.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2009", "Andreotti, G., Freeman, L. E. B., Hou, L., Coble, J., Rusiecki, J., Hoppin, J. A., Silverman, D. T., Alavanja, M. C. R.", "Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort", "", "124(10):2495-2500", "b59a980f-c20a-4860-9e49-8fd355420478", "", "Pancreatic cancer is a rapidly fatal disease that has been linked with pesticide use. Previous studies have reported excess risks of pancreatic cancer with organochlorines such as DDT, however, many other commonly used pesticides have not been examined. To further examine the potential associations between the use of a number of pesticides and pancreatic cancer, we conducted a case-control analysis in the Agricultural Health Study, one of the largest prospective cohorts with over 89,000 participants including pesticide applicators and their spouses in Iowa and North Carolina. This analysis included 93 incident pancreatic cancer cases (64 applicators, 29 spouses) and 82,503 cancer-free controls who completed an enrollment questionnaire providing detailed pesticide use, demographic and lifestyle information. Ever use of 24 pesticides and intensity-weighted lifetime days [(lifetime exposure days) x (exposure intensity score)] of 13 pesticides was assessed. Risk estimates were calculated using unconditional logistic regression controlling for age, smoking, and diabetes. Among pesticide applicators, 2 herbicides (EPTC and pendimethalin) of the 13 pesticides examined for intensity-weighted lifetime use showed a statistically significant exposure-response association with pancreatic cancer. Applicators in the top half of lifetime pendimethalin use had a 3.0-fold (95% CI 1.3-7.2, p-trend = 0.01) risk compared with never users, and those in the top half of lifetime EPTC use had a 2.56-fold (95% CI = 1.1-5.4, p-trend = 0.01) risk compared with never users. Organochlorines were not associated with an excess risk of pancreatic cancer in this study. These findings suggest that herbicides, particularly pendimethalin and EPTC, may be

associated with pancreatic cancer. © 2008 Wiley-Liss, Inc.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2010", "Andreotti, G., Hou, L., Beane Freeman, L. E., Mahajan, R., Koutros, S., Coble, J., Lubin, J., Blair, A., Hoppin, J. A., Alavanja, M.", "Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort", "", "21(11):1759-1775", "3883b27b-1ce0-4f77-81c9-fb5e7224908b", "", "Obesity is associated with increased risks of several cancers including colon and female breast. Pesticide use in agricultural populations has also been linked with higher risks of various cancers. However, the interaction between obesity and pesticide use on cancer risk has not been well studied. Using data from the Agricultural Health Study, we examined the association between body mass index (BMI) and the risk of cancer at 17 sites and the interaction between BMI and pesticide use. Pesticide applicators residing in Iowa and North Carolina and their spouses were enrolled between 1993 and 1997 and given a self-administered questionnaire to obtain pesticide use and other information. This analysis included 39,628 men and 28,319 women with height and weight data who were cancer-free at enrollment. Among these participants, 4,432 were diagnosed with cancer between enrollment and 2005 and 64% were overweight or obese. BMI (per 1 kg/m<sup>2</sup>) was positively associated with colon cancer in men (hazard ratio (HR) 1.05, 95% confidence interval (CI) 1.02-1.09) and breast cancer in postmenopausal women (HR 1.03, 95% CI 1.01-1.06). In contrast, BMI was inversely associated with lung cancer in men, with a significant association in ever smokers (HR 0.92, 95% CI 0.88-0.97) and a null association in never smokers. The positive association between BMI and colon cancer in men was significant in those who ever used carbofuran (HR = 1.10, 95% CI 1.04-1.17; p-interaction = 0.04) or metolachlor (HR = 1.09, 95% CI 1.04-1.15; p-interaction = 0.02) but was null in non-users of these pesticides. Among male ever smokers, the inverse association between BMI and lung cancer was significant in non-users of carbofuran (HR = 0.87, 95% CI = 0.82-0.92) but was null in users of carbofuran (p-interaction = 0.02). These findings suggest that certain pesticides may modify the effects of BMI on the risks of colon and lung cancers. © 2010 US Government.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "1999", "Andres-Barquin, P. J., Hernandez, M. C., Israel, M. A.", "Id4 expression induces apoptosis in astrocytic cultures and is down-regulated by activation of the cAMP-dependent signal transduction pathway", "Experimental cell research", "247(2):347-55", "8b86efed-89e2-4f77-97c5-09718a2aa8fa", "", "The Id family of helix-loop-helix transcription factors has been implicated in the regulation of cellular differentiation in several different lineages. We have explored the potential regulatory role of the cyclic AMP-dependent signaling pathway on Id gene expression in astroglial primary cultures. We found that primary cultures of mouse forebrain astrocytes constitutively expressed the four known members of the Id gene family, Id1, Id2, Id3, and Id4. During culture in presence of serum for 4 weeks, the expression of Id4 was up-regulated. In these same cultures, treatment with dibutyryl-cyclic AMP, a cyclic AMP analogue known to promote astrocyte differentiation, dramatically and selectively decreased Id4 gene expression. This effect was detectable after short-term treatment and was maintained during long-term treatment. Forskolin and pentoxifylline, two other agents known to elevate intracellular cyclic AMP through different mechanisms, also potently decreased Id4 gene expression. Furthermore, overexpression of Id4 in an astrocyte-derived cell line induced cells to round up and die by apoptosis. These results indicate that the cyclic AMP pathway acts as an

inhibitor of Id4 gene expression in astrocytes, identify a new function for Id4, and suggest that Id4 is strategically positioned in the chain of molecular events regulating astrocyte differentiation and apoptosis.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2016", "Arias, M., Hoffarth, E. R., Ishida, H., Aramini, J. M., Vogel, H. J.", "Recombinant expression, antimicrobial activity and mechanism of action of tritrpticin analogs containing fluoro-tryptophan residues", "Biochimica et biophysica acta", "1858(5):1012-23", "352d0af4-611c-4c44-97bc-8637eadf7ef2", "", "The increase in antibiotic-resistant bacterial infections has prompted significant academic research into new therapeutic agents targeted against these pathogens. Antimicrobial peptides (AMPs) appear as promising candidates, due their potent antimicrobial activity and their ubiquitous presence in almost all organisms. Tritrpticin is a member of this family of peptides and has been shown to exert a strong antimicrobial activity against several bacterial strains. Tritrpticin's main structural characteristic is the presence of three consecutive Trp residues at the center of the peptide. These residues play an important role in the activity of tritrpticin against *Escherichia coli*. In this work, a recombinant version of tritrpticin was produced in *E. coli* using calmodulin as a fusion protein expression tag to overcome the toxicity of the peptide. When used in combination with glyphosate, an inhibitor of the endogenous synthesis of aromatic amino acids, this expression system allowed for the incorporation of fluorinated Trp analogs at very high levels (>90%). The antimicrobial activity of the 4-, 5- and 6-fluoro-Trp-containing tritrpticins against *E. coli* was as strong as the activity of the native peptide. Similarly, the tritrpticin analogs exhibited comparable abilities to perturb and permeabilize synthetic lipid bilayers as well as the outer and inner membrane of *E. coli*. Furthermore, the use of (19)F NMR spectroscopy established that each individual fluoro-Trp residue interacts differently with SDS micelles, supporting the idea that each Trp in the original tritrpticin plays a different role in the perturbing/permeabilizing activity of the peptide. Moreover, our work demonstrates that the use of fluoro-Trp in solvent perturbation (19)F NMR experiments provides detailed site-specific information on the insertion of the Trp residues in biological membrane mimetics. This article is part of a Special Issue entitled: Antimicrobial peptides edited by Karl Lohner and Kai Hilpert.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2013", "Arjo, G., Portero, M., Pinol, C., Vinas, J., Matias-Guiu, X., Capell, T., Bartholomaeus, A., Parrott, W., Christou, P.", "Plurality of opinion, scientific discourse and pseudoscience: an in depth analysis of the Seralini et al. study claiming that Roundup Ready corn or the herbicide Roundup cause cancer in rats", "Transgenic research", "22(2):255-67", "b1784b4e-be5b-40f1-aadb-55b9a1b862f2", "", "A recent paper published in the journal Food and Chemical Toxicology presents the results of a long-term toxicity study related to a widely-used commercial herbicide (Roundup) and a Roundup-tolerant genetically modified variety of maize, concluding that both the herbicide and the maize varieties are toxic. Here we discuss the many errors and inaccuracies in the published article resulting in highly misleading conclusions, whose publication in the scientific literature and in the wider media has caused damage to the credibility of science and researchers in the field. We and many others have criticized the study, and in particular the manner in which the experiments were planned, implemented, analyzed, interpreted and communicated. The study appeared to sweep aside all known benchmarks of scientific good practice and,

more importantly, to ignore the minimal standards of scientific and ethical conduct in particular concerning the humane treatment of experimental animals.", "", "", "RefMan", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2012", "Asami, Y., Jang, J. H., Soung, N. K., He, L., Moon, D. O., Kim, J. W., Oh, H., Muroi, M., Osada, H., Kim, B. Y., Ahn, J. S.", "Protuboxepin A, a marine fungal metabolite, inducing metaphase arrest and chromosomal misalignment in tumor cells", "Bioorganic & medicinal chemistry", "20(12):3799-806", "cf0422d2-348d-4738-bd47-9a167ad3d353", "", "Previously we reported the identification of a new oxepin-containing diketopiperazine-type marine fungal metabolite, named protuboxepin A which showed antiproliferative activity in several cancer cell lines. In this study we elucidated the mechanism by which protuboxepin A induces cancer cell growth inhibition. Here we report that protuboxepin A induced round-up morphology, M phase arrest, and an increase in the subG(1) population in tumor cells in a dose dependent manner. Our investigations revealed that protuboxepin A directly binds to alpha,beta-tubulin and stabilizes tubulin polymerization thus disrupting microtubule dynamics. This disruption leads to chromosome misalignment and metaphase arrest which induces apoptosis in cancer. Overall, we identified protuboxepin A as a microtubule-stabilizing agent which has a distinctly different chemical structure from previously reported microtubule inhibitors. These results indicate that protuboxepin A has a potential of being a new and effective anti-cancer drug.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2008", "Asare, N., Landvik, N. E., Lagadic-Gossmann, D., Rissel, M., Tekpli, X., Ask, K., Lag, M., Holme, J. A.", "1-Nitropyrene (1-NP) induces apoptosis and apparently a non-apoptotic programmed cell death (paraptosis) in Hepalclc7 cells", "Toxicology and applied pharmacology", "230(2):175-86", "daf102e7-a050-44b9-b02b-d389053bc3e7", "", "Mechanistic studies of nitro-PAHs (polycyclic aromatic hydrocarbons) of interest might help elucidate which chemical characteristics are most important in eliciting toxic effects. 1-Nitropyrene (1-NP) is the predominant nitrated PAH emitted in diesel exhaust. 1-NP-exposed Hepalclc7 cells exhibited marked changes in cellular morphology, decreased proliferation and different forms of cell death. A dramatic increase in cytoplasmic vacuolization was observed already after 6 h of exposure and the cells started to round up at 12 h. The rate of cell proliferation was markedly reduced at 24 h and apoptotic as well as propidium iodide (PI)-positive cells appeared. Electron microscopic examination revealed that the vacuolization was partly due to mitochondria swelling. The caspase inhibitor Z-VAD-FMK inhibited only the apoptotic cell death and Nec-1 (an inhibitor of necroptosis) exhibited no inhibitory effects on either cell death or vacuolization. In contrast, cycloheximide markedly reduced both the number of apoptotic and PI-positive cells as well as the cytoplasmic vacuolization, suggesting that 1-NP induced paraptotic cell death. All the MAPKs; ERK1/2, p38 and JNK, appear to be involved in the death process since marked activation was observed upon 1-NP exposure, and their inhibitors partly reduced the induced cell death. The ERK1/2 inhibitor PD 98057 completely blocked the induced vacuolization, whereas the other MAPKs inhibitors only had minor effects on this process. These findings suggest that 1-NP may cause apoptosis and paraptosis. In contrast, the corresponding amine (1-aminopyrene) elicited only minor apoptotic and necrotic cell death, and cells with characteristics typical of paraptosis were absent.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2003", "Axelrad, J. C., Howard, C. V.,

McLean, W. G.", "The effects of acute pesticide exposure on neuroblastoma cells chronically exposed to diazinon", "Toxicology", "185(1-2):67-78", "dd5c7725-51c7-4a4b-a0a5-a9d56faff74b", "", "Speculation about potential neurotoxicity due to chronic exposure to low doses of organophosphate (OP) pesticides is not yet supported by experimental evidence. The objective of this work was to use a cell culture model of chronic OP exposure to determine if such exposure can alter the sensitivity of nerve cells to subsequent acute exposure to OPs or other compounds. NB2a neuroblastoma cells were grown in the presence of 25 microM diazinon for 8 weeks. The OP was then withdrawn and the cells were induced to differentiate in the presence of various other pesticides or herbicides, including OPs and OP-containing formulations. The resulting outgrowth of neurite-like structures was measured by light microscopy and quantitative image analysis and the IC(50) for each OP or formulation was calculated. The IC(50) values in diazinon-pre-exposed cells were compared with the equivalent values in cells not pre-exposed to diazinon. The IC(50) for inhibition of neurite outgrowth by acute application of diazinon, pyrethrum, glyphosate or a commercial formulation of glyphosate was decreased by between 20 and 90% after pre-treatment with diazinon. In contrast, the IC(50) for pirimiphos methyl was unaffected and those for phosmet or chlorpyrifos were increased by between 1.5- and 3-fold. Treatment of cells with chlorpyrifos or with a second glyphosate-containing formulation led to the formation of abnormal neurite-like structures in diazinon-pre-exposed cells. The data support the view that chronic exposure to an OP may reduce the threshold for toxicity of some, but by no means all, environmental agents.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2003", "Bai, F., Xi, J. H., Wawrousek, E. F., Fleming, T. P., Andley, U. P.", "Hyperproliferation and p53 status of lens epithelial cells derived from alphaB-crystallin knockout mice", "The Journal of biological chemistry", "278(38):36876-86", "598fc47e-ce68-4a19-b262-c583070b4394", "", "alphaB-Crystallin, a major protein of lens fiber cells, is a stress-induced chaperone expressed at low levels in the lens epithelium and numerous other tissues, and its expression is enhanced in certain pathological conditions. However, the function of alphaB in these tissues is not known. Lenses of alphaB-/- mice develop degeneration of specific skeletal muscles but do not develop cataracts. Recent work in our laboratory indicates that primary cultures of alphaB-/- lens epithelial cells demonstrate genomic instability and undergo hyperproliferation at a frequency 4 orders of magnitude greater than that predicted by spontaneous immortalization of rodent cells. We now demonstrate that the hyperproliferative alphaB-/- lens epithelial cells undergo phenotypic changes that include the appearance of the p53 protein as shown by immunoblot analysis. Sequence analysis showed a lack of mutations in the p53 coding region of hyperproliferative alphaB-/- cells. However, the reentry of hyperproliferative alphaB-/- cells into S phase and mitosis after DNA damage by gamma-irradiation were consistent with impaired p53 checkpoint function in these cells. The results demonstrate that expression of functionally impaired p53 is one of the factors that promote immortalization of lens epithelial cells derived from alphaB-/- mice. Fluorescence in situ hybridization using probes prepared from centromere-specific mouse P1 clones of chromosomes 1 and 9 demonstrated that the hyperproliferative alphaB-/- cells were 30% diploid and 70% tetraploid, whereas wild type cells were 83% diploid. Further evidence of genomic instability was obtained when the hyperproliferative alphaB-/- cells were labeled with anti-beta-tubulin antibodies. Examination of the hyperproliferative alphaB-/- mitotic profiles revealed the presence of cells that

failed to round up for mitosis, or arrested in cytokinesis, and binucleated cells in which nuclear division had occurred without cell division. These results suggest that the stress protein and molecular chaperone alphaB-crystallin protects cells from acquiring impaired p53 protein and genomic instability."

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"Unknown","Unknown","Unknown","Unknown",,"","2000","Barco, A., Feduchi, E., Carrasco, L.,"A stable HeLa cell line that inducibly expresses poliovirus 2A(pro): effects on cellular and viral gene expression","Journal of virology","74(5):2383-92","7afea819-4f1f-4b8f-951f-753bb32f1fef",,"A HeLa cell clone (2A7d) that inducibly expresses the gene for poliovirus protease 2A (2A(pro)) under the control of tetracycline has been obtained. Synthesis of 2A(pro) induces severe morphological changes in 2A7d cells. One day after tetracycline removal, cells round up and a few hours later die. Poliovirus 2A(pro) cleaves both forms of initiation factor eIF4G, causing extensive inhibition of capped-mRNA translation a few hours after protease induction. Methoxysuccinyl-Ala-Ala-Pro-Val-chloromethylketone, a selective inhibitor of 2A(pro), prevents both eIF4G cleavage and inhibition of translation but not cellular death. Expression of 2A(pro) still allows both the replication of poliovirus and the translation of mRNAs containing a picornavirus leader sequence, while vaccinia virus replication is drastically inhibited. Translation of transfected capped mRNA is blocked in 2A7d-On cells, while luciferase synthesis from a mRNA bearing a picornavirus internal ribosome entry site (IRES) sequence is enhanced by the presence of 2A(pro). Moreover, synthesis of 2A(pro) in 2A7d cells complements the translational defect of a poliovirus 2A(pro)-defective variant. These results show that poliovirus 2A(pro) expression mimics some phenotypical characteristics of poliovirus-infected cells, such as cell rounding, inhibition of protein synthesis and enhancement of IRES-driven translation. This cell line constitutes a useful tool to further analyze 2A(pro) functions, to complement poliovirus 2A(pro) mutants, and to test antiviral compounds."

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"Unknown","Unknown","Unknown","Unknown",,"","2011","Barry, K. H., Koutros, S., Berndt, S. I., Andreotti, G., Hoppin, J. A., Sandler, D. P., Burdette, L. A., Yeager, M., Freeman, L. E. B., Lubin, J. H., Ma, X., Zheng, T., Alavanja, M. C. R.,"Genetic variation in base excision repair pathway genes, pesticide exposure, and prostate cancer risk",,"119(12):1726-1732","3bdf1bfa-224e-499d-be42-f1d2a9682fdd",,"Background: Previous research indicates increased prostate cancer risk for pesticide applicators and pesticide manufacturing workers. Although underlying mechanisms are unknown, evidence suggests a role of oxidative DNA damage. Objectives: Because base excision repair (BER) is the predominant pathway involved in repairing oxidative damage, we evaluated interactions between 39 pesticides and 394 tag single-nucleotide polymorphisms (SNPs) for 31 BER genes among 776 prostate cancer cases and 1,444 male controls in a nested case-control study of white Agricultural Health Study (AHS) pesticide applicators. Methods: We used likelihood ratio tests from logistic regression models to determine p-values for interactions between three-level pesticide exposure variables (none/low/high) and SNPs (assuming a dominant model), and the false discovery rate (FDR) multiple comparison adjustment approach. Results: The interaction between fonofos and rs1983132 in NEIL3 [nei endonuclease VIII-like 3 (Escherichia coli)], which encodes a glycosylase that can initiate BER, was the most significant over-all [interaction p-value (pinteract) = 9.3 Å- 10-6; FDR-adjusted p-value = 0.01]. Fonofos exposure was associated with a monotonic increase in prostate cancer risk among

men with CT/TT genotypes for rs1983132 [odds ratios (95% confidence intervals) for low and high use compared with no use were 1.65 (0.91, 3.01) and 3.25 (1.78, 5.92), respectively], whereas fonofos was not associated with prostate cancer risk among men with the CC genotype. Carbofuran and S-ethyl dipropylthiocarbamate (EPTC) interacted similarly with rs1983132; however, these interactions did not meet an FDR < 0.2. Conclusions: Our significant finding regarding fonofos is consistent with previous AHS findings of increased prostate cancer risk with fonofos exposure among those with a family history of prostate cancer. Although requiring replication, our findings suggest a role of BER genetic variation in pesticide-associated prostate cancer risk.

["", "", "", "RefMan", "", "", "", "", "", "", "", "", "", "", "Unknown", "Unknown", "Unknown", "Unknown", "", "", "2007", "Belle, R., Le Bouffant, R., Morales, J., Cosson, B., Cormier, P., Mulner-Lorillon, O.", "[Sea urchin embryo, DNA-damaged cell cycle checkpoint and the mechanisms initiating cancer development]", "Journal de la Societe de biologie", "201(3):317-27", "41b9c440-48d5-461b-a6b3-fdfdf5822a6a", "", "Cell division is an essential process for heredity, maintenance and evolution of the whole living kingdom. Sea urchin early development represents an excellent experimental model for the analysis of cell cycle checkpoint mechanisms since embryonic cells contain a functional DNA-damage checkpoint and since the whole sea urchin genome is sequenced. The DNA-damaged checkpoint is responsible for an arrest in the cell cycle when DNA is damaged or incorrectly replicated, for activation of the DNA repair mechanism, and for commitment to cell death by apoptosis in the case of failure to repair. New insights in cancer biology lead to two fundamental concepts about the very first origin of cancerogenesis. Cancers result from dysfunction of DNA-damaged checkpoints and cancers appear as a result of normal stem cell (NCS) transformation into a cancer stem cell (CSC). The second aspect suggests a new definition of "cancer", since CSC can be detected well before any clinical evidence. Since early development starts from the zygote, which is a primary stem cell, sea urchin early development allows analysis of the early steps of the cancerization process. Although sea urchins do not develop cancers, the model is alternative and complementary to stem cells which are not easy to isolate, do not divide in a short time and do not divide synchronously. In the field of toxicology and incidence on human health, the sea urchin experimental model allows assessment of cancer risk from single or combined molecules long before any epidemiologic evidence is available. Sea urchin embryos were used to test the worldwide used pesticide Roundup that contains glyphosate as the active herbicide agent; it was shown to activate the DNA-damage checkpoint of the first cell cycle of development. The model therefore allows considerable increase in risk evaluation of new products in the field of cancer and offers a tool for the discovery of molecular markers for early diagnostic in cancer biology. Prevention and early diagnosis are two decisive elements of human cancer therapy.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", "Unknown", "Unknown", "Unknown", "Unknown", "", "", "2009", "Benachour, N., S  ralini, G. E.", "Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells", "", "22(1):97-105", "61b50d94-06ee-4cb9-986a-dc9a94a26471", "", "We have evaluated the toxicity of four glyphosate (G)-based herbicides in Roundup (R) formulations, from 105 times dilutions, on three different human cell types. This dilution level is far below agricultural recommendations and corresponds to low levels of residues in food or feed. The formulations have been compared to G alone and with its main metabolite AMPA or with one known adjuvant of R

formulations, POEA. HUVEC primary neonate umbilical cord vein cells have been tested with 293 embryonic kidney and JEG3 placental cell lines. All R formulations cause total cell death within 24 h, through an inhibition of the mitochondrial succinate dehydrogenase activity, and necrosis, by release of cytosolic adenylate kinase measuring membrane damage. They also induce apoptosis via activation of enzymatic caspases 3/7 activity. This is confirmed by characteristic DNA fragmentation, nuclear shrinkage (pyknosis), and nuclear fragmentation (karyorrhexis), which is demonstrated by DAPI in apoptotic round cells. G provokes only apoptosis, and HUVEC are 100 times more sensitive overall at this level. The deleterious effects are not proportional to G concentrations but rather depend on the nature of the adjuvants. AMPA and POEA separately and synergistically damage cell membranes like R but at different concentrations. Their mixtures are generally even more harmful with G. In conclusion, the R adjuvants like POEA change human cell permeability and amplify toxicity induced already by G, through apoptosis and necrosis. The real threshold of G toxicity must take into account the presence of adjuvants but also G metabolism and time-amplified effects or bioaccumulation. This should be discussed when analyzing the in vivo toxic actions of R. This work clearly confirms that the adjuvants in Roundup formulations are not inert. Moreover, the proprietary mixtures available on the market could cause cell damage and even death around residual levels to be expected, especially in food and feed derived from R formulation-treated crops. © 2009 American Chemical Society.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2007", "Benachour, N., Sipahutar, H., Moslemi, S., Gasnier, C., Travert, C., Seralini, G. E.", "Time- and dose-dependent effects of roundup on human embryonic and placental cells", "Archives of environmental contamination and toxicology", "53(1):126-33", "179ed1f5-da0c-4cf5-8b4e-70d14bf291f3", "", "Roundup is the major herbicide used worldwide, in particular on genetically modified plants that have been designed to tolerate it. We have tested the toxicity and endocrine disruption potential of Roundup (Bioforce on human embryonic 293 and placental-derived JEG3 cells, but also on normal human placenta and equine testis. The cell lines have proven to be suitable to estimate hormonal activity and toxicity of pollutants. The median lethal dose (LD(50)) of Roundup with embryonic cells is 0.3% within 1 h in serum-free medium, and it decreases to reach 0.06% (containing among other compounds 1.27 mM glyphosate) after 72 h in the presence of serum. In these conditions, the embryonic cells appear to be 2-4 times more sensitive than the placental ones. In all instances, Roundup (generally used in agriculture at 1-2%, i.e., with 21-42 mM glyphosate) is more efficient than its active ingredient, glyphosate, suggesting a synergistic effect provoked by the adjuvants present in Roundup. We demonstrated that serum-free cultures, even on a short-term basis (1 h), reveal the xenobiotic impacts that are visible 1-2 days later in serum. We also document at lower non-overtly toxic doses, from 0.01% (with 210 microM glyphosate) in 24 h, that Roundup is an aromatase disruptor. The direct inhibition is temperature-dependent and is confirmed in different tissues and species (cell lines from placenta or embryonic kidney, equine testicular, or human fresh placental extracts). Furthermore, glyphosate acts directly as a partial inactivator on microsomal aromatase, independently of its acidity, and in a dose-dependent manner. The cytotoxic, and potentially endocrine-disrupting effects of Roundup are thus amplified with time. Taken together, these data suggest that Roundup exposure may affect human reproduction and fetal development in case of contamination. Chemical mixtures in formulations appear to be underestimated

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D.", "Molecular identification and expression of two non-P450 enzymes, monoamine oxidase A and flavin-containing monooxygenase 2, involved in phase I of xenobiotic biotransformation in the Pacific oyster, *Crassostrea gigas*", "Biochimica et biophysica acta", "1679(1):29-36", "99add1c7-3c49-4cce-a844-ab797cbbelc3", "", "Marine bivalve metabolism can be perturbed by hydrocarbon and pesticide pollution in coastal ecosystems. In this study, in the Pacific oyster, *Crassostrea gigas*, full-length cDNAs encoding two non-P450 phase I enzymes, flavin-containing monooxygenase 2 (FMO-2) and monamine oxidase A (MAO A), were characterized. Both sequences contained the co-factor fixation motifs characteristic of their respective enzyme families. Using reverse transcription polymerase chain reaction (RT-PCR), the messenger RNA (mRNA) transcription levels of these two enzymes in tissues of oysters exposed, under experimental conditions, to hydrocarbons and two pesticide treatments were investigated. The pesticide treatments were exposure to either glyphosate or to a mixture composed of atrazine, diuron and isoproturon. The results showed a strong differential expression of FMO-2 and MAO A that was both tissue-specific as well as time- and treatment-dependent. It was also clearly demonstrated that the transcription levels of MAO A (generally considered a constitutive enzyme without external regulation) were induced by hydrocarbons and pesticides in digestive gland and inhibited by pesticides in gill tissue. Furthermore, the transcription levels of FMO-2 and MAO A mRNA in digestive gland might be useful as a marker of hydrocarbon or pesticide exposure in monitoring programs.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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after supplementing 1 mM isopropylbeta-D-thiogalactopyranoside (IPTG) in a 2 h-culture broth. Since the expressed EPSPS protein was found as an insoluble form in the inclusion body, it was extracted by 6 M urea after sonication, and then purified through immobilized nickel-affinity column chromatography to isolate EPSPS having a molecular mass of 57 kDa. When incubated in simulated gastric fluid containing pepsin at pH 1.5, the purified EPSPS protein was completely digested within 1 min. In addition, the passive cutaneous anaphylaxis reaction of the purified EPSPS protein was not observed in the Sprague Dawley rat system that was administered either orally or subcutaneously. Furthermore, treatment of the EPSPS protein to the culture of the sensitized peritoneal mast cells, or unsensitized but antisera-labeled mast cells, showed neither a remarkable change in the histamine release nor a cytokine production, including interleukin-4 (IL-4) and tumor necrosis factor-alpha (TNF-alpha). Thus, it can be concluded that the EPSPS protein in the GM soybean showed no significant allergenicity in the Sprague Dawley rats."

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2012", "Chen, H. E., Lin, J. F., Tsai, T. F., Lin, Y. C., Chou, K. Y., Hwang, T. I. S.", "Induction of autophagic cell death by allyl isothiocyanate", "", "9:132", "78d6cd32-7742-4575-86b2-8b17df9d30c4", "", "Purpose: Previous studies supported that certain food phytochemicals protect against cancer. Isothiocyanates (ITCs) are derivatives of cruciferous vegetable and shown to be effective cancer-prevention agents. Allyl isothiocyanate (AITC), one of the most widely studies members of the ITC family, has recently be demonstrate to inhibit survival of human prostate cancer cells while has minimal effects on a normal prostate epithelial cell line. Our previous studies demonstrate AITC induces autophagic cell death in human prostate cancer cells. In this study, we investigate whether the autophagy induced by AITC treatment is activated by mTOR or other signaling pathway. Materials and Methods: We investigated the biological effects of AITC on PC-3 and CRW22Rv1 (androgen-independent and sensitive human prostate cancer cell lines, respectively) on cell viability using MTT assay and induced apoptosis using cell cytometry. We further monitor the induced autophagy in AITC-treated cells by detecting the digestion and

formation of LC3-II, a marker protein involved in the formation of autophagosome during autophagic cell death, by Western blot as well as Immunofluorescent (IF) staining. The formation of acidic organelle was detected by acridine orange staining. To identify the signaling pathway involved in AITC-induced autophagy, protein expression of mTOR effector, 4EBP1 and phosphor-S6, and ERK were detected by western blot. Results: AITC exhibited significant dose and time-dependent growth inhibition on both PC-3 and CRW22Rv1 cells. The formation of LC3-II was detectable at 10  $\mu$ M, and increased at 20  $\mu$ M after 24 hours of AITC treatment. IF showed round-up and condensed staining of LC3-II, suggesting the formation of autophagosome in the cytoplasm and acridine orange staining of acidic organelles supporting this finding. Inhibition of autophagy partially rescued cell viability suggesting a protective role of autophagy in AITC-treated cells. Detection of protein levels in AITC-treated cells showed activation of ERK while mTOR signaling was not altered by BITC treatment. Conclusion: We provide evidences that AITC inhibit PC-3 and CRW22Rv1 cancer cell growth thought not only apoptosis cell death but also autophagic cell death. And the autophagy induced by AITC was via ERK activation but not mTOR inhibition. This activity could potentially contribute to the beneficial effect of AITC in prostate cancer

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2010", "Chen, H. E., Tsai, T. F., Lin, Y. C., Chou, K. Y., Hwang, T. I. S., Lin, J. F.", "Allyl isothiocyanate, a constituent of cruciferous vegetables, induces autophagic death in human prostate cancer cells", "", "17:A165", "6dd5250e-1ce7-4e78-a861-e1831d9f7ae8", "", "Purpose: Cruciferous vegetable-derived isothiocyanates (ITCs) has shown to be an effective cancer-prevention agent. Allyl isothiocyanate (AITC), one of the most widely studies members of the ITC family, has recently be demonstrate to inhibit survival of human prostate cancer cells while has minimal effects on a normal prostate epithelial cell line. In this study, we investigate whether the growth inhibition is cause by program cell death pathways. Materials and methods: We have investigated the biological effects of AITC on PC-3 and CRW22Rv1 ( and rogen-ind ependent and sensitive human prostate cancer cell lines, respectively) cell survival by MTT assay. We investegated the digestion and formation of LC3-II, a marker protein involved in the formation of autophagosome during autophagic cell death, by Western blot as well as Immunofluorescent (IF) staining. The formation of acidic organelle was detected by acridine orange staining. Results: AITC exhibited significant dose and time-dependent growth inhibition on both PC-3 and CRW22Rv1 cells. The formation of LC3-II was detectable at 10p.M, and increased at 20p.M after 72hours of AITC treatment. IF showed round-up and condensed staining of LC3-II, suggesting the formation of autophagosome in the cytoplasm and acridine orange staining of acidic organelles supporting this finding. Conclusion: AITC markedly inhibit PC-3 and CRW22Rv1 cancer cell growth thought not only apoptosis cell death but also autophagic cell death. This activity could potentially contribute to the beneficial effect of AITC in prostate cancer patients.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2013", "Chorfa, A., Betemps, D., Morignat, E., Lazizzera, C., Hogeveen, K., Andrieu, T., Baron, T.", "Specific pesticide-dependent increases in alpha-synuclein levels in human neuroblastoma (SH-SY5Y) and melanoma (SK-MEL-2) cell lines", "Toxicological sciences : an official journal of the Society of Toxicology", "133(2):289-97", "e9a1920c-2658-47a8-be19-069bea18e304", "", "Epidemiological studies indicate a role of genetic and environmental factors in Parkinson's disease involving alterations of the neuronal alpha-synuclein (alpha-syn) protein. In particular, a relationship between Parkinson's disease and occupational exposure to pesticides has been repeatedly suggested. Our objective was to precisely assess changes in alpha-syn levels in human neuroblastoma (SH-SY5Y) and melanoma (SK-MEL-2) cell lines following acute exposure to pesticides (rotenone, paraquat, maneb, and glyphosate) using Western blot and flow cytometry. These human cell lines express alpha-syn endogenously, and overexpression of alpha-syn (wild type or mutated A53T) can be obtained following recombinant adenoviral transduction. We found that endogenous alpha-syn levels in the SH-SY5Y neuroblastoma cell line were markedly increased by paraquat, and to a lesser extent by rotenone and maneb, but not by glyphosate. Rotenone also clearly increased endogenous alpha-syn levels in the SK-MEL-2 melanoma cell line. In the SH-SY5Y cell line, similar differences were observed in the alpha-syn adenovirus-transduced cells, with a higher increase of the A53T mutated protein. Paraquat markedly increased alpha-syn in the SK-MEL-2 adenovirus-transduced cell line, similarly for the wild-type or A53T proteins. The observed differences in the propensities of pesticides to increase alpha-syn levels are in agreement with numerous reports that indicate a potential role of exposure to certain pesticides in the development of Parkinson's disease. Our data support the hypothesis that pesticides can trigger some molecular events involved in this disease and also in

malignant melanoma that consistently shows a significant but still unexplained association with Parkinson's disease.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2014", "Coalova, I., Rios de Molina Mdel, C., Chaufan, G.", "Influence of the spray adjuvant on the toxicity effects of a glyphosate formulation", "Toxicology in vitro : an international journal published in association with BIBRA", "28(7):1306-11", "17718135-90b5-433b-a686-74dfb93d7c42", "", "In the present study, the influence of the spray adjuvant on the toxicity effects of a glyphosate formulation was examined in HEp-2 cell line. We determined the median lethal concentration (LC50) of Atanor(R) (glyphosate formulation), Impacto(R) (spray adjuvant) and the mixture of both agrochemicals. We also compared the toxicities of the pesticides individually and in mixture and we analyzed the effects on oxidative balance from each treatment. Our results showed that all the agrochemicals assayed induce dose and time-dependent cytotoxicity and that the toxicity of Impacto(R) with Atanor(R) (mixture) was additive on HEp-2 cell line. All the agrochemicals assayed produced an increase in catalase activity and glutathione levels, while no effects were observed for superoxide dismutase and glutathione-S-transferase activities. We found an important increase in ROS production in cells treated with Atanor(R) and mixture. Besides, all the agrochemicals used triggered caspase 3/7 activation and hence induced apoptosis pathway in this cell line. In conclusion, our results demonstrated that the addition of adjuvant to glyphosate formulation increase the toxicity of the mixture in cell culture. Furthermore, cell culture exposed to agrochemical mixture showed an increased ROS production and antioxidant defenses.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2001", "Cowan, C. A., Henkemeyer, M.", "The SH2/SH3 adaptor Grb4 transduces B-ephrin reverse signals", "Nature", "413(6852):174-9", "af60af8f-245c-4eab-b7cb-4a51d52fc52c", "", "Bidirectional signals mediated by membrane-anchored ephrins and Eph receptor tyrosine kinases have important functions in cell-cell recognition events, including those that occur during axon pathfinding and hindbrain segmentation. The reverse signal that is transduced into B-ephrin-expressing cells is thought to involve

tyrosine phosphorylation of the signal's short, conserved carboxy-terminal cytoplasmic domain. The Src-homology-2 (SH2) domain proteins that associate with activated tyrosine-phosphorylated B-subclass ephrins have not been identified, nor has a defined cellular response to reverse signals been described. Here we show that the SH2/SH3 domain adaptor protein Grb4 binds to the cytoplasmic domain of B ephrins in a phosphotyrosine-dependent manner. In response to B-ephrin reverse signalling, cells increase FAK catalytic activity, redistribute paxillin, lose focal adhesions, round up, and disassemble F-actin-containing stress fibres. These cellular responses can be blocked in a dominant-negative fashion by expression of the isolated Grb4 SH2 domain. The Grb4 SH3 domains bind a unique set of other proteins that are implicated in cytoskeletal regulation, including the Cbl-associated protein (CAP/ponsin), the Abl-interacting protein-1 (Abi-1), dynamin, PAK1, hnRNPk and axin. These data provide a biochemical pathway whereby cytoskeletal regulators are recruited to Eph-ephrin bidirectional signalling complexes.

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 "Unknown", "Unknown", "Unknown", "Unknown", "", "", "1996", "Crenshaw, H. C., Allen, J. A., Skeen, V., Harris, A., Salmon, E. D.", "Hydrostatic pressure has different effects on the assembly of tubulin, actin, myosin II, vinculin, talin, vimentin, and cytokeratin in mammalian tissue cells", "Experimental cell research", "227(2):285-97", "fa326669-0108-4263-a62e-cfad62d0aea4", "", "Hydrostatic pressures in the range of hundreds of atmospheres are known to disrupt cytoskeletal organization in tissue culture cells, with profound changes in cell shape. The molecular mechanisms of these effects are poorly understood. To determine the effect of pressure on the cytoskeleton, and thus to provide better indicators of the molecular mechanisms, we used fluorescent antibody staining to compare the organizations of seven different cytoskeletal proteins in HeLa cells and rat osteosarcoma cells (ROS-17/2.8) subjected to different pressures up to 400 atm. Pressures of 300 atm or more caused cells of both lines to ""round up"" and to withdraw their lamellar extensions. However, this response varied within a population of cells, with some cells remaining spread at pressures that caused their neighbors to round up. The most resistant to rounding were those cells touching other cells, and the occasional giant cells. As expected, the rounded cells showed disruption of actin stress fibers and of vinculin and talin at focal contacts. The unrounded cells showed less disruption in the organization of these same proteins. Microtubules and myosin II filaments appeared resistant to 400 atm pressure in both cell types, whether rounded or unrounded. However, in HeLa cells, the intermediate filaments, vimentin and cytokeratin, depolymerized and formed small vesicles when pressures exceeded 200 atm, and this occurred in rounded as well as unrounded cells. In osteosarcoma cells, which do not have cytokeratin, vimentin did not depolymerize. We discuss different mechanisms that might explain these responses to pressure, including direct effects on the equilibria of protein polymerization and less direct effects on regulatory mechanisms, such as phosphorylation pathways, that control cytoskeletal organization. The later type of explanation seems more consistent with both the variability of response within cell populations and the difference in vimentin's response in one cell line compared with the other.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""  
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chemicals for their potential to cause developmental neurotoxicity. Use of in vitro neuronal models, including human cells, is one approach that allows for timely, cost-effective toxicity screening. The present study compares the sensitivity of human (ReN CX) and mouse (mCNS) neuroprogenitor cell lines to chemicals using a multiplex assay for proliferation and apoptosis, endpoints that are critical for neural development. Cells were exposed to 0.001-100 µM concentrations of 11 chemicals (cadmium, chlorpyrifos oxon, dexamethasone, dieldrin, ketamine, lead, maneb, methylmercury, nicotine, trans-retinoic acid, and trimethyltin) reported in the literature to affect proliferation and/or apoptosis, and 5 chemicals (dimethyl phthalate, glyphosate, omeprazole, saccharin, and d-sorbitol) with no reports of effects on either endpoint. High-content screening of markers for proliferation (BrdU incorporation) and apoptosis (activated caspase 3 and p53) was used to assess the effect of chemicals in both cell lines. Of the chemicals tested, methylmercury, cadmium, dieldrin, chlorpyrifos oxon, trans-retinoic acid, and trimethyltin decreased proliferation by at least 50% of control in either the ReN CX or mCNS cells. None of the chemicals tested activated caspase 3 or p53 in the ReN CX cells, while methylmercury, cadmium, dieldrin, chlorpyrifos oxon, trimethyltin, and glyphosate all induced at least a doubling in these apoptotic markers in the mCNS cells. Compared to control, cadmium, trans-retinoic acid, and trimethyltin decreased cell viability (ATP levels) by at least 50% in the ReN CX cells, while cadmium, dieldrin, and methylmercury decreased viability by at least 50% in the mCNS cells. Based on these results, BrdU is an appropriate marker for assessing chemical effects on proliferation, and human cells are more sensitive than mouse cells for this endpoint. By contrast, caspase 3 and p53 were altered by environmental chemicals in mouse, but not in human cells. Therefore, these markers are not appropriate to assess the ability of environmental chemicals to induce apoptosis in the ReN CX cells."

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 "Unknown","Unknown","Unknown","Unknown","","","2014","Dabrowski, J. M., Shadung, J. M., Wepener, V.,"Prioritizing agricultural pesticides used in South Africa based on their environmental mobility and potential human health effects","","62:31-40","6db3704f-7ca2-44d6-9729-9167fc0b12aa","","South Africa is the largest user of pesticides in sub-Saharan Africa and many studies have highlighted the occurrence of pesticides in water resources. Poor management of water treatment facilities in combination with a relatively high dependency on untreated water from boreholes and rivers creates the potential for exposure of human communities to pesticides and their associated health effects. Pesticide use, physicochemical and toxicity data was therefore used to prioritize pesticides in terms of their potential risk to human health. After eliminating pesticides used in very low quantities, four indices were used to prioritize active ingredients applied in excess of 1000. kg per annum; the quantity index (QI) which ranked pesticides in terms of the quantity of their use; the toxicity potential index (TP) which ranked pesticides according to scores derived for their potential to cause five health effects (endocrine disruption, carcinogenicity, teratogenicity, mutagenicity and neurotoxicity); hazard potential index (HP) which multiplied the TP by an exposure potential score determined by the GUS index for each pesticide (to provide an indication of environmental hazard); and weighted hazard potential (WHP), which multiplied the HP for a pesticide by the ratio of its use to the total use of all pesticides in the country. The top 25 pesticides occurring in each of these indices were identified as priority pesticides, resulting in a combined total of 69 priority pesticides. A principal component analysis identified the indices that were

most important in determining why a specific pesticide was included in the final priority list. As crop specific application pesticide use data was available it was possible to identify crops to which priority pesticides were applied to. Furthermore it was possible to prioritize crops in terms of the specific pesticide applied to the crop (by expressing the WHP as a ratio of the total amount of pesticide applied to the crop to the total use of all pesticides applied in the country). This allows for an improved spatial assessment of the use of priority pesticides. The methodology applied here provides a first level of basic, important information that can be used to develop monitoring programmes, identify priority areas for management interventions and to investigate optimal mitigation strategies. © 2013 Elsevier

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lamella, temporarily preventing lamellar extension and forward movement of the cell. With increasing culture time, there is an increase in apparent adhesion and a corresponding marked decrease in locomotory velocity. Under these conditions, high doses of RGD/mAb do not cause keratocytes to detach or even produce detectable lamellar instabilities. We postulate that RGD/mAb competitively inhibits new beta1 integrin mediated adhesion formation that is required to support the rates of lamellar extension necessary for rapid locomotion.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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sensitivity was the same, but the specificity was higher in the NELSON trial relative to the NLST: 98.3% vs. 73.4%. The positive predictive value was in our trial (40.4%) substantially higher than in other trials: f.e. 3.8% in the NLST(2). Furthermore, our findings showed that the 2 year-probability of developing lung cancer for all included participants was 1.3% (1.2-1.5) (8). For screened participants without any nodules this probability (more than half of the included participants) was 0.4%, which suggests that a screening interval of at least two years might be safe to apply in these individuals. In all participants with CT-detected nodules, lung cancer probability was 2.5% (2.1-2.9) but individuals' probabilities depended strongly on nodule volume, diameter and VDT. New data: the last screening round, which took place 2.5 years after the third round, showed 46 screen-detected lung cancers, of which 58.7% were diagnosed at stage I and 23.8% at stage III/IV. More squamous-cell carcinomas (21.7% vs. 16.3%), small cell carcinomas (6.5% vs. 3.8%) and bronchioalveolar carcinomas (8.7% vs. 5.3%) were detected compared to the first three screening rounds. However, relative to the first three rounds the lung cancer detection rate was lower (0.80 vs 0.80-1.1) and lung cancer was detected at a more advanced stage (stage III/IV; 23.8% vs 8.1). Currently, we are working on the review of blinded medical files of the deceased participants to determine the cause of death, and we are collecting medical data of control arm participants. (Figure Presented).

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environment", "371(1-3):44-54", "07159d61-3062-428b-8834-9680ff57d006", "", "We integrated an index-based attenuation factor/retardation factor (AF/RF) model into a GIS to evaluate the risk of leaching of the most frequently applied herbicides (glyphosate, diuron, diquat, bromacil, simazine, linuron, terbuthylazine, and terbumeton) used in citrus orchards of the Valencia Community, Spain. The GIS-model system was applied to a region of 33,800 ha located near Valencia City. The soil and climate data required by the model were stored in an Arc/Info GIS in which the model algorithms were integrated using the AML programming language. A graphical user interface was developed to facilitate the use of the GIS-model system. The resulting simulation maps indicate that terbumeton, bromacil, and simazine herbicides have the highest risk of leaching because of their high mobility and low K(oc) (32-158 mg l(-1)). The remaining herbicides are strongly adsorbed by clay particles and organic matter, thus minimising the risk of leaching through the soil profile and into groundwater. The obtained ranking of the leaching potential of analysed herbicides is as follows, from highest to lowest risk: terbumeton>bromacil>simazine>terbuthylazine>diuron>linuron>glyphosate>diquat.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2005", "De Roos, A. J., Blair, A., Rusiecki, J. A., Hoppin, J. A., Svec, M., Dosemeci, M., Sandler, D. P., Alavanja, M. C.", "Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study", "Environmental health perspectives", "113(1):49-54", "9c6251aa-1d3f-476f-a107-3802e8dc4af1", "", "Glyphosate is a broad-spectrum herbicide that is one of the most frequently applied pesticides in the world. Although there has been little consistent evidence of genotoxicity or carcinogenicity from in vitro and animal studies, a few epidemiologic reports have indicated potential health effects of glyphosate. We evaluated associations between glyphosate exposure and cancer incidence in the Agricultural Health Study (AHS), a prospective cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. Detailed information on pesticide use and other factors was obtained from a self-administered questionnaire completed at time of enrollment (1993-1997). Among private and commercial applicators, 75.5% reported having ever used glyphosate, of which > 97% were men. In this analysis, glyphosate exposure was defined as a) ever personally mixed or applied products containing glyphosate; b) cumulative lifetime days of use, or ""cumulative exposure days"" (years of use times days/year); and c) intensity-weighted cumulative exposure days (years of use times days/year times estimated intensity level). Poisson regression was used to estimate exposure-response relations between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtypes. Glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes we studied. There was a suggested association with multiple myeloma incidence that should be followed up as more cases occur in the AHS. Given the widespread use of glyphosate, future analyses of the AHS will allow further examination of long-term health effects, including less common cancers.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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the 1980s, the National Cancer Institute conducted three case-control studies of NHL in the midwestern United States. These pooled data were used to examine pesticide exposures in farming as risk factors for NHL in men. The large sample size (n = 3417) allowed analysis of 47 pesticides simultaneously, controlling for potential confounding by other pesticides in the model, and adjusting the estimates based on a prespecified variance to make them more stable. RESULTS: Reported use of several individual pesticides was associated with increased NHL incidence, including organophosphate insecticides coumaphos, diazinon, and fonofos, insecticides chlordane, dieldrin, and copper acetoarsenite, and herbicides atrazine, glyphosate, and sodium chlorate. A subanalysis of these ""potentially carcinogenic"" pesticides suggested a positive trend of risk with exposure to increasing numbers. CONCLUSION: Consideration of multiple exposures is important in accurately estimating specific effects and in evaluating realistic exposure scenarios.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Djikić Rom, A., Jotanović, J., Andrejević, M., Micev, M.", "The controversy of signet ring cell degeneration of gallbladder mucosa", "", "467(1):S226", "67834837-6b60-4bcc-9e16-207295d8c617", "", "Objective: Signet ring cell degeneration (SRCP) is a phenomenon of epithelial cells to round up and shape making signet ring forms considered to be degenerative change. It is emphasized that there is a high risk of overdiagnosis of signet ring cell adenocarcinoma in same locations. The precise mechanism for their production is still unclear, but it seems to be related to ischemia, necrosis, ulceration or provoked by inflammatory process. Method: Routine histological, histochemical (alcian blue, PAS) and ancillary immunohistochemical (E-cadherin, Ki-67, p53) examination were done. Results: We present a case of 76-year-old male patient who had chronic perforated pyloric ulcer and had cholecystectomy due to prominent surrounding peritonitis. Besides chronic cholecystitis, mucosa showed almost completely SRCD accompanied by papillary hyperplasia with focal low grade dysplasia. Although almost all epithelial cells expressed strong membranous immunopositivity for E-cadherin, some group of significantly atypical dysplastic epithelial cells showed high Ki-67 and p53 index associated with SRCD. Conclusion: This rare and peculiar SRCD phenomenon is not always mucosal degeneration of non-neoplastic cells and could be associated with dysplasia.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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sphingomyelin it induces a high level of TNF-alpha release which is significantly increased by incubation with non-inactivated serum. Ceramide phosphate also induces TNF-alpha release in J774A.1 cells, but (unlike sphingomyelin/sphingomyelinase) the level of release is not influenced by the presence or otherwise of non-inactivated serum. L. gaucho venom does not induce proliferation of J774A.1 cells and even at high concentrations it does not affect their viability. J774A.1 cells, which prior to venom treatment were elongated and clumped, round up after venom treatment, but, revert to their original morphology after incubation with fresh medium. TNF-alpha resistant MRC-5 cells and TNF-alpha sensitive MCF-7 cells are susceptible to the toxic effect of both L. gaucho venom and ceramide phosphate. The results obtained in this study demonstrate that exogenous sphingomyelin can modulate, in vitro, the release of TNF-alpha induced by L. gaucho venom in mouse macrophages. In addition, the results also indicate that ceramide phosphate and L. gaucho venom are toxic to several different cell types, via a variety of mechanisms, some, but not all, of which may involve TNF-alpha as an intermediary.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2003", "Duke, S. O., Rimando, A. M., Pace, P. F., Reddy, K. N., Smeda, R. J.", "Isoflavone, glyphosate, and aminomethylphosphonic acid levels in seeds of glyphosate-treated, glyphosate-resistant soybean", "Journal of agricultural and food chemistry", "51(1):340-4", "2b74a8e8-ef69-44bf-a675-8bfa4524b4d5", "", "The estrogenic isoflavones of soybeans and their glycosides are products of the shikimate pathway, the target pathway of glyphosate. This study tested the hypothesis that nonphytotoxic levels of glyphosate and other herbicides known to affect phenolic compound biosynthesis might influence levels of these nutraceutical compounds in glyphosate-resistant soybeans. The effects of glyphosate and other herbicides were determined on estrogenic isoflavones and shikimate in glyphosate-resistant soybeans from identical experiments conducted on different cultivars in Mississippi and Missouri. Four commonly used herbicide treatments were compared to a hand-weeded control. The herbicide treatments were (1) glyphosate at 1260 g/ha at 3 weeks after planting (WAP), followed by glyphosate at 840 g/ha at 6 WAP; (2) sulfentrazone at 168 g/ha plus chlorimuron at 34 g/ha applied preemergence (PRE), followed by glyphosate at 1260 g/ha at 6 WAP; (3) sulfentrazone at 168 g/ha plus chlorimuron at 34 g/ha applied PRE, followed by glyphosate at 1260 g/ha at full bloom; and (4) sulfentrazone at 168 g/ha plus chlorimuron at 34 g/ha applied PRE, followed by acifluorfen at 280 g/ha plus bentazon at 560 g/ha plus clethodim at 140 g/ha at 6 WAP. Soybeans were harvested at maturity, and seeds were analyzed for daidzein, daidzin, genistein, genistin, glycitin, glycitein, shikimate, glyphosate, and the glyphosate degradation product, aminomethylphosphonic acid (AMPA). There were no remarkable effects of any treatment on the contents of any of the biosynthetic compounds in soybean seed from either test site, indicating that early and later season applications of glyphosate have no effects on phytoestrogen levels in glyphosate-resistant soybeans. Glyphosate and AMPA residues were higher in seeds from treatment 3 than from the other two treatments in which glyphosate was used earlier. Intermediate levels were found in treatments 1 and 2. Low levels of glyphosate and AMPA were found in treatment 4 and a hand-weeded control, apparently due to herbicide drift.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

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4c75-8212-9cf63c917c6d", "", "Glyphosate is the active ingredient and polyoxyethyleneamine, the major component, is the surfactant present in the herbicide Roundup formulation. The objective of this study was to analyze potential cytotoxicity of the Roundup and its fundamental substance (glyphosate). Albino male rats were intraperitoneally treated with sub-lethal concentration of Roundup (269.9mg/kg) or glyphosate (134.95mg/kg) each 2 days, during 2 weeks. Hepatotoxicity was monitored by quantitative analysis of the serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) activities, total protein, albumin, triglyceride and cholesterol. Creatinine and urea were used as the biochemical markers of kidney damages. The second aim of this study to investigate how glyphosate alone or included in herbicide Roundup affected hepatic reduced glutathione (GSH) and lipid peroxidation (LPO) levels of animals as an index of antioxidant status and oxidative stress, respectively, as well as the serum nitric oxide (NO) and alpha tumour necrosis factor (TNF-alpha) were measured. Treatment of animals with Roundup induced the leakage of hepatic intracellular enzymes, ALT, AST and ALP suggesting irreversible damage in hepatocytes starting from the first week. It was found that the effects were different on the enzymes in Roundup and glyphosate-treated groups. Significant time-dependent depletion of GSH levels and induction of oxidative stress in liver by the elevated levels of LPO, further confirmed the potential of Roundup to induce oxidative stress in hepatic tissue. However, glyphosate caused significant increases in NO levels more than Roundup after 2 weeks of treatment. Both treatments increased the level of TNF-alpha by the same manner. The results suggest that excessive antioxidant disruptor and oxidative stress is induced with Roundup than

glyphosate.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

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coordinate daughter cell adhesion with cytokinesis", "The Journal of cell biology", "201(5):709-24", "6ae4d9ae-314a-4f49-9bc0-fa3b8b4b54a8", "", "During mitosis, human cells round up, decreasing their adhesion to extracellular substrates. This must be quickly reestablished by poorly understood cytoskeleton remodeling mechanisms that prevent detachment from epithelia, while ensuring the successful completion of cytokinesis. Here we show that the microtubule end-binding (EB) proteins EB1 and EB3 play temporally distinct roles throughout cell division. Whereas EB1 was involved in spindle orientation before anaphase, EB3 was required for stabilization of focal adhesions and coordinated daughter cell spreading during mitotic exit. Additionally, EB3 promoted midbody microtubule stability and, consequently, midbody stabilization necessary for efficient cytokinesis. Importantly, daughter cell adhesion and cytokinesis completion were spatially regulated by distinct states of EB3 phosphorylation on serine 176 by Aurora B. This EB3 phosphorylation was enriched at the midbody and shown to control cortical microtubule growth. These findings uncover differential roles of EB proteins and explain the importance of an Aurora B phosphorylation gradient for the spatiotemporal regulation of microtubule function during mitotic exit and cytokinesis.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", "Unknown", "Unknown", "Unknown", "Unknown", "", "", "2006", "Finkelstein, J. B.", "Cancer legislation roundup", "", "3(7):456-461", "b3ff9bf3-f036-4817-97e9-4b5144a762bd", "", "", "", "", "RefMan", "", "", "", "", "", "", "", "", "Unknown", "Unknown", "Unknown", "Unknown", "", "", "2014", "Fischer-Friedrich, E., Hyman, A. A., Julicher, F., Muller, D. J., Helenius, J.", "Quantification of surface tension and internal pressure generated by single mitotic cells", "Scientific reports", "4:6213", "8f52845b-81ce-4485-b8cd-78660f68b50b", "", "During mitosis, adherent cells round up, by increasing the tension of the contractile actomyosin cortex while increasing the internal hydrostatic pressure. In the simple scenario of a liquid cell interior, the surface tension is related to the local curvature and the hydrostatic pressure difference by Laplace's law. However, verification of this scenario for cells requires accurate measurements of cell shape. Here, we use wedged micro-cantilevers to uniaxially confine single cells and determine confinement forces while concurrently determining cell shape using confocal microscopy. We fit experimentally measured confined cell shapes to shapes obeying Laplace's law with uniform surface tension and find quantitative agreement. Geometrical parameters derived from fitting the cell shape, and the measured force were used to calculate hydrostatic pressure excess and surface tension of cells. We find that HeLa cells increase their internal hydrostatic pressure excess and surface tension from approximately 40 Pa and 0.2 mNm(-1) during interphase to approximately 400 Pa and 1.6 mNm(-1) during metaphase. The method introduced provides a means to determine internal pressure excess and surface tension of rounded cells accurately and with minimal cellular perturbation, and should be applicable to characterize the mechanical properties of various cellular systems.", "", "", "RefMan", "", "", "", "", "", "", "", "", "Unknown", "Unknown", "Unknown", "Unknown", "", "", "2011", "Forgacs, A. L., Ding, Q., Huhtaniemi, I. T., Rahman, N. A., Zacharewski, T. R.", "BLTK1 murine Leydig tumor cells: A novel model for evaluating the steroidogenic effects of reproductive and developmental toxicants", "", "28:90", "5e8a7826-1520-454b-ae54-2281bc9f5050", "", "Leydig cells are the primary site of androgen steroid hormone biosynthesis in males, which is necessary for proper reproductive development and function. Several environmental toxicants target Leydig cell steroidogenesis, resulting in both developmental and

reproductive effects including testicular dysgenesis syndrome. BLTK1 cells, a novel murine Leydig cell line (BLT- 1 cells, clone K1), possess an intact steroidogenic pathway producing low basal levels of testosterone (T), and express all the necessary steroidogenic enzymes including Star, Cyp11a1, Cyp17a1, Hsd3b1 and Hsd17b3 as confirmed by RT-PCR and/or Western blot analysis. In addition, 3 ng/ml recombinant human chorionic gonadotropin (rhCG) induced cAMP ( $\sim 100$ -fold), progesterone (P,  $\sim 10$ -fold) and testosterone (T,  $\sim 10$ -fold) compared to basal levels, as well as induced Cyp17a1 and Hsd17b3 mRNA levels. Dose-dependent and temporal studies of the effects of triazine herbicides, phthalates (di- and monoesters), triclosan and glyphosate on steroidogenic activity in BLK1 cells suggest different modes of action underlying altered steroidogenesis, with varying potency and efficacy as reflected in treatment-specific gene expression profiles. These studies suggest BLTK1 cells are not only a suitable in vitro model to screen chemical libraries for effects on steroidogenesis, but can also be used to elucidate the mechanisms underlying their endocrine disrupting effects.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2012", "Forgacs, A. L., Ding, Q., Jaremba, R. G., Huhtaniemi, I. T., Rahman, N. A., Zacharewski, T. R.", "BLTK1 murine Leydig cells: a novel steroidogenic model for evaluating the effects of reproductive and developmental toxicants", "Toxicological sciences : an official journal of the Society of Toxicology", "127(2):391-402", "5ebfa685-e3f2-47cf-b3b9-98b4a92e0eee", "", "Leydig cells are the primary site of androgen biosynthesis in males. Several environmental toxicants target steroidogenesis resulting in both developmental and reproductive effects including testicular dysgenesis syndrome. The aim of this study was to evaluate the effect of several structurally diverse endocrine disrupting compounds (EDCs) on steroidogenesis in a novel BLTK1 murine Leydig cell model. We demonstrate that BLTK1 cells possess a fully functional steroidogenic pathway that produces low basal levels of testosterone (T) and express all the necessary steroidogenic enzymes including Star, Cyp11a1, Cyp17a1, Hsd3b1, Hsd17b3, and Srd5a1. Recombinant human chorionic gonadotropin (rhCG) and forskolin (FSK) elicited concentration- and time-dependent induction of 3',5'-cyclic adenosine monophosphate, progesterone (P), and T, as well as the differential expression of Star, Hsd3b6, Hsd17b3, and Srd5a1 messenger RNA levels. The evaluation of several structurally diverse male reproductive toxicants including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), atrazine, prochloraz, triclosan, monoethylhexyl phthalate (MEHP), glyphosate, and RDX in BLTK1 cells suggests different modes of action perturb steroidogenesis. For example, prochloraz and triclosan antifungals reduced rhCG induction of T, consistent with published in vivo data but did not alter basal T levels. In contrast, atrazine and MEHP elicited modest induction of basal T but antagonized rhCG-mediated induction of T levels, whereas TCDD, glyphosate, and RDX had no effect on basal or rhCG induction of T in BLTK1 cells. These results suggest that BLTK1 cells maintain rhCG-inducible steroidogenesis and are a viable in vitro Leydig cell model to evaluate the effects of EDCs on steroidogenesis. This model can also be used to elucidate the different mechanisms underlying toxicant-mediated disruption of steroidogenesis.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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Occupational and Environmental Medicine", "58(4):370-5", "5b1757a7-3044-4ec1-9b9e-2dc0f0a686c7", "", "OBJECTIVE: The objective of the study was to examine the association between occupational exposure to pesticides and cutaneous melanoma, controlling for all possible confounders. METHODS: A pooled analysis of two case-control studies was conducted in two different geographic areas (Italy and Brazil). Detailed pesticides exposure histories were obtained. RESULTS: Ever use of any pesticide was associated with a high risk of cutaneous melanoma (odds ratio 2.58; 95% confidence interval 1.18-5.65) in particular exposure to herbicides (glyphosate) and fungicides (mancozeb, maneb), after controlling for confounding factors. When subjects were exposed to both pesticides and occupational sun exposure, the risk increased even more (odds ratio 4.68; 95% confidence interval 1.29-17.0). CONCLUSIONS: The study suggests an augmented risk of cutaneous melanoma among subjects with exposure to pesticides, in particular among those exposed to occupational sun exposure.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2014", "Garlich, F. M., Goldman, M., Pepe, J., Nelson, L. S., Allan, M. J., Goldstein, D. A., Goldfarb, D. S., Hoffman, R. S.", "Hemodialysis clearance of glyphosate following a life-threatening ingestion of glyphosate-surfactant herbicide", "", "52(1):66-71", "46841f10-0374-4faa-bacd-fbe3d54b49d4", "", "Context. Ingestion of glyphosate-surfactant herbicides (GlySH) can result in acute kidney injury, electrolyte abnormalities, acidosis, cardiovascular collapse, and death. In severe toxicity, the use of hemodialysis is reported, but largely unsupported by kinetic analysis. We report the dialysis clearance of glyphosate following a suicidal ingestion of a glyphosate-containing herbicide. Case details. A 62-year-old man was brought to the emergency department (ED) 8.5 h after drinking a bottle of commercial herbicide containing a 41% solution of glyphosate isopropylamine, in polyoxyethyleneamine (POEA) surfactant and water. He was bradycardic and obtunded with respiratory depression necessitating intubation and mechanical ventilation. Initial laboratory results were significant for the following: pH, 7.11; PCO2, 64 mmHg; PO2, 48 mmHg; potassium, 7.8 mEq/L; Cr 3.3, mg/dL; bicarbonate, 22 mEq/L; anion gap, 18

mEq/L; and lactate, 7.5 mmol/L. Acidosis and hyperkalemia persisted despite ventilation and fluid resuscitation. The patient underwent hemodialysis 16 h post ingestion, after which he demonstrated resolution of acidosis and hyperkalemia, and improvement in clinical status. Serum glyphosate concentrations were drawn prior to, during, and after hemodialysis. The extraction ratio and hemodialysis clearance were calculated to be 91.8% and 97.5 mL/min, respectively. Discussion. We demonstrate the successful clearance of glyphosate using hemodialysis, with corresponding clinical improvement in a patient with several poor prognostic factors (advanced age, large volume ingested, and impaired consciousness). The effects of hemodialysis on the surfactant compound are unknown. Hemodialysis can be considered when severe acidosis and acute kidney injury complicate ingestion of glyphosate-containing products. © 2014 Informa Healthcare USA, Inc.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2009", "Gasnier, C., Dumont, C., Benachour, N., Clair, E., Chagnon, M. C., Seralini, G. E.", "Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines", "Toxicology", "262(3):184-91", "c27a5f65-dc51-4a8f-9c96-33cc05772cd6", "", "Glyphosate-based herbicides are the most widely used across the world; they are commercialized in different formulations. Their residues are frequent pollutants in the environment. In addition, these herbicides are spread on most eaten transgenic plants, modified to tolerate high levels of these compounds in their cells. Up to 400 ppm of their residues are accepted in some feed. We exposed human liver HepG2 cells, a well-known model to study xenobiotic toxicity, to four different formulations and to glyphosate, which is usually tested alone in chronic in vivo regulatory studies. We measured cytotoxicity with three assays (Alamar Blue, MTT, ToxiLight), plus genotoxicity (comet assay), anti-estrogenic (on ERalpha, ERbeta) and anti-androgenic effects (on AR) using gene reporter tests. We also checked androgen to estrogen conversion by aromatase activity and mRNA. All parameters were disrupted at sub-agricultural doses with all formulations within 24h. These effects were more dependent on the formulation than on the glyphosate concentration. First, we observed a human cell endocrine disruption from 0.5 ppm on the androgen receptor in MDA-MB453-kb2 cells for the most active formulation (R400), then from 2 ppm the transcriptional activities on both estrogen receptors were also inhibited on HepG2. Aromatase transcription and activity were disrupted from 10 ppm. Cytotoxic effects started at 10 ppm with Alamar Blue assay (the most sensitive), and DNA damages at 5 ppm. A real cell impact of glyphosate-based herbicides residues in food, feed or in the environment has thus to be considered, and their classifications as carcinogens/mutagens/reprotoxics is discussed.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2010", "Ge, X., d'Avignon, D. A., Ackerman, J. J., Sammons, R. D.", "Rapid vacuolar sequestration: the horseweed glyphosate resistance mechanism", "Pest management science", "66(4):345-8", "e7f303ec-f93e-451b-ae0f-940333b793c9", "", "BACKGROUND: Glyphosate-resistant (GR) weed species are now found with increasing frequency and threaten the critically important glyphosate weed-management system [corrected]. RESULTS: The reported (31)P NMR experiments on glyphosate-sensitive (S) and glyphosate-resistant (R) horseweed, Conyza canadensis (L.) Cronq., show significantly more accumulation of glyphosate within the R biotype vacuole. CONCLUSIONS: Selective sequestration of glyphosate into the vacuole confers the observed horseweed resistance to glyphosate. This observation represents the first clear evidence for the glyphosate resistance mechanism in C. canadensis.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2010", "George, J., Prasad, S., Mahmood, Z., Shukla, Y.", "Studies on glyphosate-induced carcinogenicity in mouse skin: a proteomic approach", "Journal of proteomics", "73(5):951-64", "26d2c243-47a7-46cc-ab35-fbbd76d20e39", "", "Glyphosate is a widely used broad spectrum herbicide, reported to induce various toxic effects in non-target species, but its carcinogenic potential is still unknown. Here we showed the carcinogenic effects of glyphosate using 2-stage mouse skin carcinogenesis model and proteomic analysis. Carcinogenicity study revealed that glyphosate has tumor promoting activity. Proteomic analysis using 2-dimensional gel electrophoresis and mass spectrometry showed that 22 spots were differentially expressed (>2 fold) on glyphosate, 7, 12-dimethylbenz[*a*]anthracene (DMBA) and 12-O-tetradecanoyl-phorbol-13-acetate (TPA) application over untreated control. Among them, 9 proteins (translation elongation factor eEF-1 alpha chain, carbonic anhydrase III, annexin II, calcyclin, fab fragment anti-VEGF antibody, peroxiredoxin-2, superoxide dismutase [Cu-Zn], stefin A3, and calgranulin-B) were common and showed similar expression pattern in glyphosate and TPA-treated mouse skin. These proteins are known to be involved in several key processes like apoptosis and growth-inhibition, anti-oxidant responses, etc. The up-regulation of calcyclin, calgranulin-B and down-regulation of superoxide dismutase [Cu-Zn] was further confirmed by immunoblotting, indicating that these proteins can be good candidate biomarkers for skin carcinogenesis induced by glyphosate. Altogether, these results suggested that glyphosate has tumor promoting potential in skin carcinogenesis and its mechanism seems to be similar to TPA.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2011", "George, J., Shukla, Y.", "Pesticides and cancer: Insights into toxicoproteomic-based findings", "", "74(12):2713-2722", "b7cb2b12-0bf7-4bdc-a50a-0bbfba08b239", "", "Humans are often exposed to a variety of pollutants that contribute to an individual's risk for diseases including cancer. Animal, cell cultures and epidemiological lines of evidence demonstrate that exposure to various environmental pollutants including pesticides are associated with increasing frequency of cancers. Organophosphates, organochlorines, carbamates, pyrethroids, the major groups of pesticides, have been reported to be carcinogenic in various models. However, the results of these studies are still controversial, nevertheless, their mechanism of action is clear. Therefore, new strategies in toxicological research are needed for efficient screening for adverse effects of pesticides on complex living systems. Biomarkers can be employed to identify causal associations and to make better quantitative and qualitative estimates of those associations at relevant levels of exposure. This will enable us to deepen our understanding of mechanism behind their carcinogenic potential. Deciphering the associations between pesticide exposure and cancer, following toxicoproteomics application, will be useful in the development of potential predictive biomarkers of pesticide induced carcinogenicity. Therefore, the thrust of this article was to review the risk of cancer due to pesticide exposure and significant toxicoproteomic-based studies conducted so far, to identify the novel molecules as possible biomarkers for cancer following pesticide exposure. Â© 2011 Elsevier B.V.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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that glyphosate possesses tumor promoting potential in mouse skin carcinogenesis and SOD 1, calcyclin (S100A6), and calgranulin B (S100A9) have been associated with this potential, although the mechanism is unclear. We aimed to clarify whether imbalance in between [Ca(2+)] i levels and oxidative stress is associated with glyphosate-induced proliferation in human keratinocytes HaCaT cells. The [Ca(2+)] i levels, ROS generation, and expressions of G1/S cyclins, IP3R1, S100A6, S100A9, and SOD 1, and apoptosis-related proteins were investigated upon glyphosate exposure in HaCaT cells. Glyphosate (0.1 mM) significantly induced proliferation, decreases [Ca(2+)] i , and increases ROS generation in HaCaT cells, whereas antioxidant N-acetyl-L-cysteine (NAC) pretreatment reverts these effects which directly indicated that glyphosate induced cell proliferation by lowering [Ca(2+)] i levels via ROS generation. Glyphosate also enhanced the expression of G1/S cyclins associated with a sharp decrease in G0/G1 and corresponding increase in S-phases. Additionally, glyphosate also triggers S100A6/S100A9 expression and decreases IP3R1 and SOD 1 expressions in HaCaT cells. Notably, Ca(2+) suppression also prevented apoptotic related events including Bax/Bcl-2 ratio and caspases activation. This study highlights that glyphosate promotes proliferation in HaCaT cells probably by disrupting the balance in between [Ca(2+)] i levels and oxidative stress which in turn facilitated the downregulation of mitochondrial apoptotic signaling pathways.

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Giuffrida, M. C., Zanolì, L. M., D'Agata, R., Finotti, A., Gambari, R., Spoto, G.", "Isothermal circular-strand-displacement polymerization of DNA and microRNA in digital microfluidic devices", "Analytical and bioanalytical chemistry", "407(6):1533-43", "e2a3b569-30bd-4791-9f6f-f5c1b371c158", "", "Nucleic-acid amplification is a crucial step in nucleic-acid-sequence-detection assays. The use of digital microfluidic devices to miniaturize amplification techniques reduces the required sample volume and the analysis time and offers new possibilities for process automation and integration in a single device. The recently introduced droplet polymerase-chain-reaction (PCR) amplification methods require repeated cycles of two or three temperature-dependent steps during the amplification of the nucleic-acid target sequence. In contrast, low-temperature isothermal-amplification methods have no need for thermal cycling, thus requiring simplified microfluidic-device features. Here, the combined use of digital microfluidics and molecular-beacon (MB)-assisted isothermal circular-strand-displacement polymerization (ICSDP) to detect microRNA-210 sequences is described. MicroRNA-210 has been described as the most consistently and predominantly upregulated hypoxia-inducible factor. The nmol L(-1)-pmol L(-1) detection capabilities of the method were first tested by targeting single-stranded DNA sequences from the genetically modified Roundup Ready soybean. The ability of the droplet-ICSDP method to discriminate between full-matched, single-mismatched, and unrelated sequences was also investigated. The detection of a range of nmol L(-1)-pmol L(-1) microRNA-210 solutions compartmentalized in nanoliter-sized droplets was performed, establishing the ability of the method to detect as little as 10(-18) mol of microRNA target sequences compartmentalized in 20 nL droplets. The suitability of the method for biological samples was tested by detecting microRNA-210 from transfected K562 cells."

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between mouse and fish micronucleus test using cyclophosphamide, mitomycin C and various pesticides", "Mutation research", "518(2):145-50", "159f0a4c-89f7-4b22-a4f4-84bdfef81822", "", "A comparative analysis between mouse and fish erythrocyte micronuclei (MN) assays was carried out using cyclophosphamide, mitomycin C and various pesticides such as alliete, brestanid, decis 25 CE (deltamethrin), kelthane 480 CE (dicofol), roundup (glyphosate), imazapyr and thiram. The aim of this study was to evaluate the fish species *Tilapia rendalli* as a suitable organism for the detection of genotoxicants in water. The clastogens cyclophosphamide and mitomycin C induced MN in both test-systems. Insecticides: decis 25 CE increased *T. rendalli* MN frequencies at doses of 1.0 and 5.0mg/kg, but not at the highest dose, and in mice there was no MN induction. Kelthane 480 CE also induced a significant MN frequency in *T. rendalli*, but not in mice. Fungicides: alliete and brestanid induced MN only in *T. rendalli*, while thiram was negative in both assays. Herbicides: imazapyr induced MN in *T. rendalli* at the maximum tolerated dose only, while roundup induced MN at three dosed levels. In mice both herbicides presented negative results. This study revealed that fish MN assay can be used as a genotoxicological test-system since some methodological particularities were observed.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2013", "Guha, N., Ward, M. H., Gunier, R., Colt, J. S., Suzanne Lea, C., Buffer, P. A., Metayer, C.", "Characterization of residential pesticide use and chemical formulations through self-report and household inventory: The northern California childhood leukemia study", "", "121(2):276-282", "c99873f0-5475-4d54-9db8-d2e28ac1119a", "", "Background: Home and garden pesticide use has been linked to cancer and other health outcomes in numerous epidemiological studies. Exposure has generally been self-reported, so the assessment is potentially limited by recall bias and lack of information on specific chemicals. oB je c t i v e s: As part of an integrated assessment of residential pesticide exposure, we identified active ingredients and described patterns of storage and use. Methods: During a home interview of 500 residentially stable households enrolled in the Northern California Childhood Leukemia Study during 2001-2006, trained interviewers inventoried residential pesticide products and queried participants about their storage and use. U.S. Environmental Protection Agency registration numbers, recorded from pesticide product labels, and pesticide chemical codes were matched to public databases to obtain information on active ingredients and chemical class. Poisson regression was used to identify independent predictors of pesticide storage. Analyses were restricted to 259 participating control households. results: Ninety-five percent (246 of 259) of the control households stored at least one pesticide product (median, 4). Indicators of higher sociodemographic status predicted more products in storage. We identified the most common characteristics: storage areas (garage, 40%; kitchen, 20%), pests treated (ants, 33%; weeds, 20%), pesticide types (insecticides, 46%; herbicides, 24%), chemical classes (pyrethroids, 77%; botanicals, 50%), active ingredients (pyrethrins, 43%) and synergists (piperonyl butoxide, 42%). Products could contain multiple active ingredients. Conclusions: Our data on specific active ingredients and patterns of storage and use will inform future etiologic analyses of residential pesticide exposures from self-reported data, particularly among households with young

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "1996", "Haendel, M. A., Bollinger, K. E., Baas, P. W.", "Cytoskeletal changes during neurogenesis in cultures of avian neural crest cells", "Journal of neurocytology", "25(4):289-301", "993e21d7-fa10-4bff-ad07-1888ee60d307", "", "Neural crest cells are motile and mitotic, whereas their neuronal derivatives are terminally post-mitotic and consist of stationary cell body from which processes grow. The present study documents changes in the cytoskeleton that occur during neurogenesis in cultures of avian neural crest cells. The undifferentiated neural crest cells contain dense bundles of actin filaments throughout their cytoplasm, and a splayed array of microtubules attached to the centrosome. In newly differentiating neurons, the actin bundles are disrupted and most of the remaining actin filaments are reorganized into a cortical layer underlying the plasma membrane of the cell body and processes. Microtubules are more abundant in newly-differentiating neurons than in the undifferentiated cells, and individual microtubules can be seen dissociated from the centrosome. Neuron-specific beta-III tubulin appears in some crest cells prior to cessation of motility and cell division, and expression increases with total microtubule levels during neurogenesis. To investigate how these early cytoskeletal changes might contribute to alterations in morphology during neurogenesis,

we have disrupted the cytoskeleton with pharmacologic agents. Microfilament disruption by cytochalasin immediately arrests the movement of neural crest cells and causes them to round-up, but does not significantly change the morphology of the immature neurons. Microtubule depolymerization by nocodazole slows the movement of undifferentiated cells and causes retraction of processes extended by the immature neurons. These results suggest that changes in the actin and microtubule arrays within neural crest cells govern distinct aspects of their morphogenesis into

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2002", "Hardell, L., Eriksson, M., Nordstrom, M.", "Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies", "Leukemia & lymphoma", "43(5):1043-9", "9e7ae97b-cb31-4092-8cb4-d06a4a100722", "", "Increased risk for non-Hodgkin's lymphoma (NHL) following exposure to certain pesticides has previously been reported. To further elucidate the importance of phenoxyacetic acids and other pesticides in the etiology of NHL a pooled analysis was performed on two case-control studies, one on NHL and another on hairy cell leukemia (HCL), a rare subtype of NHL. The studies were population based with cases identified from cancer registry and controls from population registry. Data assessment was ascertained by questionnaires supplemented over the telephone by specially trained interviewers. The pooled analysis of NHL and HCL was based on 515 cases and 1141 controls. Increased risks in univariate analysis were found for subjects exposed to herbicides (OR 1.75, CI 95% 1.26-2.42), insecticides (OR 1.43, CI 95% 1.08-1.87), fungicides (OR 3.11, CI 95% 1.56-6.27) and

impregnating agents (OR 1.48, CI 95% 1.11-1.96). Among herbicides, significant associations were found for glyphosate (OR 3.04, CI 95% 1.08-8.52) and 4-chloro-2-methyl phenoxyacetic acid (MCPA) (OR 2.62, CI 95% 1.40-4.88). For several categories of pesticides the highest risk was found for exposure during the latest decades before diagnosis. However, in multivariate analyses the only significantly increased risk was for a heterogeneous category of other herbicides than

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human neuroblastoma cell lines by the enediyne natural product neocarzinostatin", "The Journal of pharmacology and experimental therapeutics", "275(1):479-85", "948c83a3-c76c-4c59-b4f7-36a700ee3594", "", "Neocarzinostatin (NCS) is a naturally occurring enediyne antitumor agent that produces single- and double-strand breaks in cellular DNA. We have previously shown that treatment of human (SK-N-SH) and murine (NB41A3) neuroblastoma cells with NCS results in cell death for a subpopulation within the culture. The remaining cells undergo mitotic arrest with morphological differentiation along glial lines. Further investigation of cell death induced by this agent demonstrates that within 24 hr after a single one hr exposure to submicromolar concentrations of NCS, susceptible cells of both lines decrease in size, round up, detach from the culture surface and fragment in the overlying medium. This cytotoxicity is attenuated by the addition of cycloheximide (in NB41A3 cells) or aurintricarboxylic acid (in NB41A3 and SK-N-SH cells). Fluorescence and electron microscopic examination of the nonadherent cells reveals the chromatin condensation and fragmentation characteristic of apoptosis. Examination of the time course of DNA cleavage reveals that despite the presence of alkaline elution-detectable DNA cleavage, oligonucleosomal-sized DNA fragments are not demonstrable by gel electrophoresis immediately after a 1-hr incubation with the drug (1.6-10,000 nM). However, by 6 hr after treatment, DNA ladders are in evidence at all concentrations of NCS. These results suggest that the oligonucleosomal cleavage of DNA seen after NCS treatment is associated with apoptosis, rather than being the direct result of the strand-cleaving effects of the drug

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7011", "00029529-8b96-4294-82be-08fe9609ff72", "", "How the division axis is determined in mammalian cells embedded in three-dimensional (3D) matrices remains elusive, despite that many types of cells divide in 3D environments. Cells on two-dimensional (2D) substrates typically round up completely to divide. Here, we show that in 3D collagen matrices, mammalian cells such as HT1080 human fibrosarcoma and MDA-MB-231 breast cancer cells exhibit division modes distinct from their Counterparts on 2D substrates, with a markedly higher fraction of cells remaining highly elongated through mitosis in 3D matrices. The long axis of elongated mitotic cells accurately predicts the division axis, independently of matrix density and cell-matrix interactions. This 3D-specific elongated division mode is determined by the local confinement produced by the matrix and the ability of cells to protrude and locally remodel the matrix via beta1 integrin. Elongated division is readily recapitulated using collagen-coated microfabricated channels. Cells depleted of beta1 integrin still divide in the elongated mode in microchannels, suggesting that 3D confinement is sufficient to induce the elongated cell-division phenotype.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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activity to 33% of control values dramatically reduces the number of neurites per cell within 3 days of culture. The cells round up, cluster and eventually die. On the contrary, another antibody that had no significant effect on enzyme activity affected neither nerve growth factor-induced neurite formation nor survival of PC12 cells. Addition of adenosine (200 nM, 10 or 20 microM) to the culture medium did not influence PC12 cell differentiation. The effects induced by the inhibitory antibody could be only partially prevented by simultaneous application of adenosine. Our results suggest that 5'-nucleotidase is essential for nerve growth factor-induced neurite outgrowth and survival of PC12 cells. (ABSTRACT TRUNCATED AT 250

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mitosis.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown","Unknown","Unknown","Unknown","","","2014","Henneberger, P. K., Liang, X., London, S. J., Umbach, D. M., Sandler, D. P., Hoppin, J. A.", "Exacerbation of symptoms in agricultural pesticide applicators with asthma", "International archives of occupational and environmental health", "87(4):423-32", "ed72d44b-e740-4255-b340-6103a8de31a9", "", "PURPOSE: Exacerbation is a critical event in asthma management. We investigated whether exacerbation of symptoms is associated with farming exposures among agricultural pesticide applicators with asthma. METHODS: Participants were pesticide applicators with active asthma (wheezing and breathing problems in past 12 months) who completed enrollment questionnaires for the Agricultural Health Study (AHS). Exacerbation of asthma was defined as having visited a hospital emergency room or doctor for an episode of wheezing or whistling in the past 12 months. Exposures of interest were using 36 specific pesticides in the past 12 months and conducting various agricultural activities. Adjusted odds ratios (ORs) were estimated by logistic regression while controlling for potential confounders. RESULTS: The 926 AHS adult pesticide applicators with active asthma included 202 (22%) with exacerbation. Inverse associations with exacerbation were observed for two herbicides [glyphosate, odds ratio (OR) = 0.5, 95% confidence interval (CI) 0.3, 0.8, and paraquat, OR = 0.3, 95% CI 0.1, 0.9] and several agricultural activities (repairing engines, grinding metal, driving diesel tractors, and performing veterinary procedures). Only asthma cases with

allergies (i.e., doctor-diagnosed hay fever or eczema, 46%) had positive exacerbation-pesticide associations, with OR = 2.1 (95% CI 1.1, 4.1) for the herbicide pendimethalin and OR = 10.2 (95% CI 1.9, 55) for the insecticide aldicarb. CONCLUSIONS: The inverse associations with two pesticides and specific farm activities are consistent with the possibility that asthma cases prone to exacerbation may avoid exposures that trigger symptoms. Although limited by small sample size and a cross-sectional design, our study suggests that use of specific pesticides may contribute to exacerbation of asthma among individuals with allergies.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2012", "Heu, C., Berquand, A., Elie-Caille, C., Nicod, L.", "Glyphosate-induced stiffening of HaCaT keratinocytes, a Peak Force Tapping study on living cells", "Journal of structural biology", "178(1):1-7", "386b5ac3-9fe7-4260-b934-fe446f7b18b4", "", "The skin is the first physiological barrier, with a complex constitution, that provides defensive functions against multiple physical and chemical aggressions. Glyphosate is an extensively used herbicide that has been shown to increase the risk of cancer. Moreover there is increasing evidence suggesting that the mechanical phenotype plays an important role in malignant transformation. Atomic force microscopy (AFM) has emerged within the last decade as a powerful tool for providing a nanometer-scale resolution imaging of biological samples. Peak Force Tapping (PFT) is a newly released AFM-based investigation technique allowing extraction of chemical and mechanical properties from a wide range of samples at a relatively high speed and a high resolution. The present work uses the PFT technology to investigate HaCaT keratinocytes, a human epidermal cell line, and offers an original approach to study chemically-induced changes in the cellular mechanical properties under near-physiological conditions. These experiments indicate glyphosate induces cell membrane stiffening, and the appearance of cytoskeleton structures at a subcellular level, for low cytotoxic concentrations whereas cells exposed to IC50 (inhibitory concentration 50%) treatment exhibit control-like mechanical behavior despite obvious membrane damages. Quercetin, a well-known antioxidant, reverses the glyphosate-induced mechanical phenotype.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2008", "Heydens, W. F., Healy, C. E., Hotz, K. J., Kier, L. D., Martens, M. A., Wilson, A. G., Farmer, D. R.", "Genotoxic potential of glyphosate formulations: mode-of-action investigations", "Journal of agricultural and food chemistry", "56(4):1517-23", "45639083-cb9c-4126-a02a-da2d0f8c3661", "", "A broad array of in vitro and in vivo assays has consistently demonstrated that glyphosate and glyphosate-containing herbicide formulations (GCHF) are not genotoxic. Occasionally, however, related and contradictory data are reported, including findings of mouse liver and kidney DNA adducts and damage following intraperitoneal (ip) injection. Mode-of-action investigations were therefore undertaken to determine the significance of these contradictory data while concurrently comparing results from ip and oral exposures. Exposure by ip injection indeed produced marked hepatic and renal toxicity, but oral administration did not. The results suggest that ip injection of GCHF may induce secondary effects mediated by local toxicity rather than genotoxicity. Furthermore, these results continue to support the conclusion that glyphosate and GCHF are not genotoxic under exposure conditions that are relevant to animals and humans.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Hofmann, J. N., Beane Freeman, L. E., Lynch, C. F., Andreotti, G., Thomas, K. W., Sandler, D. P., Savage, S. A., Alavanja, M. C.", "The Biomarkers of Exposure and Effect in Agriculture (BEEA) Study: Rationale, Design, Methods, and Participant Characteristics", "Journal of toxicology and environmental health. Part A", "78(21-22):1338-47", "fae0902e-f772-45cc-9e96-28e72f04f39a", "", "Agricultural exposures including pesticides, endotoxin, and allergens have been associated with risk of various cancers and other chronic diseases, although the biological mechanisms underlying these associations are generally unclear. To facilitate future molecular epidemiologic investigations, in 2010 the study of Biomarkers of Exposure and Effect in Agriculture (BEEA) was initiated within the Agricultural Health Study, a large prospective cohort in Iowa and North Carolina. Here the design and methodology of BEEA are described and preliminary frequencies for participant characteristics and current agricultural exposures are reported. At least 1,600 male farmers over 50 years of age will be enrolled in the BEEA study. During a home visit, participants are asked to complete a detailed interview about recent agricultural exposures and provide samples of blood, urine, and (since 2013) house dust. As of mid-September 2014, in total, 1,233 participants have enrolled. Most of these participants (83%) were still farming at the time of interview. Among those still farming, the most commonly reported crops were corn (81%) and soybeans (74%), and the most frequently noted animals were beef cattle (35%) and hogs (13%). There were 861 (70%) participants who reported occupational pesticide use in the 12 months prior to interview; among these participants, the most frequently noted herbicides were glyphosate (83%) and 2,4-D (72%), and most commonly reported insecticides were malathion (21%), cyfluthrin (13%), and permethrin (12%). Molecular epidemiologic investigations within BEEA have the potential to yield important new insights into the biological mechanisms through which these or other agricultural exposures influence disease risk.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2011", "Hohenadel, K., Harris, S. A., McLaughlin, J. R., Spinelli, J. J., Pahwa, P., Dosman, J. A., Demers, P. A., Blair, A.", "Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces", "", "8(6):2320-2330", "21c34946-da7f-4595-80f8-67c229e7e9e9", "", "Non-Hodgkin lymphoma (NHL) has been linked to several agricultural exposures, including some commonly used pesticides. Although there is a significant body of literature examining the effects of exposure to individual pesticides on NHL, the impact of exposure to multiple pesticides or specific pesticide combinations has not been explored in depth. Data from a six-province Canadian case-control study conducted between 1991 and 1994 were analyzed to investigate the relationship between NHL, the total number of pesticides used and some common pesticide combinations. Cases (n = 513) were identified through hospital records and provincial cancer registries and controls (n = 1,506), frequency matched to cases by age and province of residence, were obtained through provincial health records, telephone listings, or voter lists. In multiple logistic regression analyses, risk of NHL increased with the number of pesticides used. Similar results were obtained in analyses restricted to herbicides, insecticides and several pesticide classes. Odds ratios increased further when only potentially carcinogenic pesticides were considered (OR[one pesticide] = 1.30, 95% CI = 0.90-1.88; OR[two to four] = 1.54, CI = 1.11-2.12; OR[five or more] = 1.94, CI = 1.17-3.23). Elevated risks were also found among those reporting use of malathion in combination with several other pesticides. These analyses support and extend previous findings that

the risk of NHL increases with the number of pesticides used and some pesticide combinations. © 2011 by the authors; licensee MDPI, Basel, Switzerland.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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uterus.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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herbicides are among the most widely used pesticides in the world. We compared the acute toxicity of the glyphosate end-use formulation Roundup Original to four North American amphibian species (*Rana clamitans*, *R. pipiens*, *R. sylvatica*, and *Bufo americanus*) and the toxicity of glyphosate technical, the polyethoxylated tallowamine surfactant (POEA) commonly used in glyphosate-based herbicides, and five newer glyphosate formulations to *R. clamitans*. For *R. clamitans*, acute toxicity values in order of decreasing toxicity were POEA > Roundup Original > Roundup Transorb > Glyphos AU; no significant acute toxicity was observed with glyphosate technical material or the glyphosate formulations Roundup Biactive, Touchdown, or Glyphos BIO. Comparisons between the four amphibian species showed that the toxicity of Roundup Original varied with species and developmental stage. *Rana pipiens* tadpoles chronically exposed to environmentally relevant concentrations of POEA or glyphosate formulations containing POEA showed decreased snout-vent length at metamorphosis and increased time to metamorphosis, tail damage, and gonadal abnormalities. These effects may be caused, in some part, by disruption of hormone signaling, because thyroid hormone receptor beta mRNA transcript levels were elevated by exposure to formulations containing glyphosate and POEA. Taken together, the data suggest that surfactant composition must be considered in the evaluation of toxicity of glyphosate-based

herbicides.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2007", "Hultberg, M.", "Cysteine turnover in human cell lines is influenced by glyphosate", "Environmental toxicology and pharmacology", "24(1):19-22", "c84830cd-4d42-43e2-ac4a-3888e30b06de", "", "Pesticides are widely spread in the environment and there is a lack of knowledge concerning the impact of these substances on the human cell. In the present study the effect of low doses of the pesticides bentazon, metalaxyl and glyphosate on the cellular metabolism of glutathione and cysteine was examined in HeLa and hepatoma cell cultures. No effect was observed when the cells were exposed to bentazon or metalaxyl. However, significant changes in the intra- and extracellular concentration of cysteine, a precursor for glutathione synthesis, were detected when glyphosate was added to the medium. This finding was observed in the presence of micromolar concentration range of glyphosate, and is relevant when compared to concentrations observed in monitoring programmes.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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antimalarial chemotherapy. © 2014 Bentham Science Publishers.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2003", "Jander, G., Baerson, S. R., Hudak, J. A., Gonzalez, K. A., Gruys, K. J., Last, R. L.", "Ethylmethanesulfonate saturation mutagenesis in Arabidopsis to determine frequency of herbicide resistance", "Plant physiology", "131(1):139-46", "3e10135f-c15d-4476-a8b2-c5f0cb66d849", "", "Plant resistance to glyphosate has been reported far less frequently than resistance to sulfonylurea and imidazolinone herbicides. However, these studies tend to be anecdotal, without side by side comparisons for a single species or natural isolate. In this study, we tested the frequencies of resistance of three herbicides in a controlled ethylmethanesulfonate (EMS) saturation mutagenesis experiment, allowing a direct comparison of the frequencies at which resistant mutant plants arise. The 100% growth inhibition dose rates of glyphosate, chlorsulfuron (a sulfonylurea herbicide), and imazethapyr (an imidazolinone herbicide) were determined for Arabidopsis. Populations of EMS-mutagenized M(2) seedlings were sprayed with twice the 100% growth inhibition dose of glyphosate, chlorsulfuron, or imazethapyr, and herbicide-resistant mutants were identified. Although there were no glyphosate-resistant mutants among M(2) progeny of 125,000 Columbia and 125,000 Landsberg erecta M(1) lines, chlorsulfuron resistance and imazethapyr resistance each appeared at frequencies of  $3.2 \times 10^{-5}$ . Given the observed frequency of herbicide resistance mutations, we calculate that there are at least 700 mutations in each EMS-mutagenized Arabidopsis line and that fewer than 50,000 M(1) lines are needed to have a 95% chance of finding a mutation in any given G:C base pair in the genome. As part of this study, two previously unreported Arabidopsis mutations conferring resistance to imidazolinone herbicides, csrl-5 (Ala-122-Thr) and csrl-6 (Ala-205-Val), were discovered. Neither of these mutations caused enhanced resistance to chlorsulfuron in Arabidopsis.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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PI(4,5)P2 levels inhibit Ras activity, supporting a negative feedback loop. Cells lacking PLC and treated with PI3K inhibitors are still able to reduce PI(4,5)P2 levels and break symmetry when receptors are activated, suggesting that other 4' or 5' phosphatases are activated by chemoattractant and contribute to "cell frontness", providing yet another level of redundancy. During cytokinesis, PM PI(4,5)P2 levels rise uniformly as cells round up at metaphase and contribute to the rounding up of the cell. These intermediate levels help reset polarity. PI(4,5)P2 levels subsequently rise in the furrow and are lowered at the poles triggering differential actin assembly, largely through localizing factors specific to the activity of the Rho GTPases, with Arp2/3 mediated filaments forming at the poles. Stimulating metaphase PTEN null cells with chemoattractant gives a transient PI(3,4,5)P3 and F-actin response. Interestingly, lack of PTEN leads to elevation of PI(3,4,5)P3 levels, but they are still regulated in response to chemoattractants at metaphase, suggesting that the threshold for Ras activity is different at this stage. These findings have important implications for cancer. Therapeutic strategies should consider targeting a host of enzymes that regulate PI(4,5)P2 levels, as cancers with low PM PI(4,5)P2 are likely to be highly metastatic. We have suggested that PI 4' and 5' Kinases help terminate uniform chemoattractant-induced responses and contribute to the "cell backness" of migrating cells. The enzymatic activity that regulates increased PM PI(4,5)P2 levels is likely the inhibition component in the Local Excitation/Global Inhibition model that we have proposed regulates chemotaxis. The responses seen during a global stimulation and the spatial distribution of signaling molecules when cells are in a chemical gradient may be explained largely by changes in PM PI(4,5)P2 levels, which influence actin assembly and cell morphology.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

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and individual pesticides suggest that these may be MM risk factors. What's new? This study is the first to investigate the risk of multiple myeloma from exposure to multiple pesticides using two distinct metrics: number of pesticides and days per year of pesticide use. Focusing on multiple pesticide exposures is important because it more accurately reflects how exposures occur in agricultural settings. Although the overall pattern was complex, increased risks observed for certain pesticide groups and individual compounds suggest that these may be risk factors for multiple myeloma.

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Y., Chung, D. I., Kong, H. H.", "Autophagy protein 12 plays an essential role in Acanthamoeba encystation", "Experimental parasitology", "159:46-52", "dee9ec7f-3d6a-44d7-823d-64728e7115e3", "", "Autophagy is a well conserved, catabolic process in eukaryotic cells. Previously, we identified two novel ubiquitin like conjugation systems (Atg12 and Atg8) in the autophagy process of Acanthamoeba castellanii. To obtain more specific information on the Atg12 ubiquitin like conjugation system during encystation of Acanthamoeba, we characterized the function of Atg12. Knockdown of AcAtg12 in trophozoites resulted in inhibition of cyst formation. Analysis of subcellular localization showed that AcAtg12 was evenly distributed in the trophozoites during early encystation, started to accumulate partially as dots or fragments, and then co-localized with the vesicle of the autophagic structure. However, the mRNA expression of AcAtg12 was maintained at a constant level during encystation as well as in trophozoites. Ultrastructural analysis with TEM showed that AcAtg12-knockdown cells showed vacuolization, lack of cyst wall formation, and numerical decline of autophagic structures, compared with the control cells. Interestingly, these knockdown cells began to round-up and swell, and then burst at 144 h post encystation. Taken together, our results might provide a better understanding of the Atg12 UBL conjugation system in Acanthamoeba and other cyst forming protozoan

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vitro : an international journal published in association with BIBRA", "27(1):191-7", "5e75f857-04f4-4de8-8647-e7cebe38a29a", "", "Glyphosate, a common herbicide, is not toxic under normal exposure circumstances. However, this chemical, when combined with a surfactant, is cytotoxic. In this study, the mechanism of the additive effect of glyphosate and TN-20, a common surfactant in glyphosate herbicides, was investigated. After exposure of rat H9c2 cells to glyphosate and TN-20 mixtures, following assays were performed: flow cytometry to determine the proportion of cells that underwent apoptosis and necrosis; western blotting to determine expression of mitochondrial proteins (Bcl-2 and Bax); immunological methods to evaluate translocation of cytochrome C; luminometric measurements to determine activity of caspases 3/7 and 9; and

tetramethyl rhodamine methyl ester assay to measure mitochondrial membrane potentials. Bcl-1 intensity decreased while Bax intensity increased with exposure to increasing TN-20 and/or glyphosate concentrations. Caspase activity increased and mitochondrial membrane potential decreased only when the cells were exposed to a mixture of both TN-20 and glyphosate, but not after exposure to either one of these compounds. The results support the possibility that mixtures of glyphosate and TN-20 aggravate mitochondrial damage and induce apoptosis and necrosis. Throughout this process, TN-20 seems to disrupt the integrity of the cellular barrier to glyphosate uptake, promoting glyphosate-mediated toxicity."

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blotting after a few hours; PKC-epsilon was down-regulated much more slowly but PKCs delta, zeta and iota were not influenced by 48 h exposure of cells to TPA. Formation of phosphatidylethanol in the transphosphatidylation reaction was markedly reduced in TPA down-regulated cells indicating a role for PKCs alpha and beta in phospholipase D activation in CG-4 line oligodendrocytes.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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2015", "Critical reviews in oncology/hematology", "", "7e7f31d2-d357-4201-99e2-1fdf40ef34ae", "", "2015 was marked by the tsunami of immune checkpoint inhibitors revealed by numerous FDA approvals, publications and abstracts in relation with these drugs in different cancers and settings. First, we reported all new indications of anti-CTLA4 and anti-PD1 approved by the FDA, the positive clinical trials published and the abstracts with promising results at important scientific meetings during 2015. Then, we discussed different critical issues of these new agents going from their predictive factors, combination therapies, tumor response patterns, efficacy in particular settings, side effect management to cost and economic burden.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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spindle morphogenesis under conditions of confinement. Using different methods to limit mitotic cell height, we show that a failure to round up causes defects in spindle assembly, pole splitting, and a delay in mitotic progression. These defects can be rescued by increasing microtubule lengths and therefore appear to be a direct consequence of the limited reach of mitotic centrosome-nucleated microtubules. These findings help to explain why most animal cells round up as they enter

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2007", "Lash, T. L.", "Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty", "Journal of occupational medicine and toxicology (London, England)", "2:15", "400d3a9f-6fc0-4b8e-b78f-2a1dc4e060ad", "", "BACKGROUND: The associations of pesticide exposure with disease outcomes are estimated without the benefit of a randomized design. For this reason and others, these studies are susceptible to systematic errors. I analyzed studies of the associations between alachlor and glyphosate exposure and cancer incidence, both derived from the Agricultural Health Study cohort, to quantify the bias and uncertainty potentially attributable to systematic error. METHODS: For each study, I identified the prominent result and important sources of systematic error that might affect it. I assigned probability distributions to the bias parameters that allow quantification of the bias, drew a value at random from each assigned distribution, and calculated the estimate of effect adjusted for the biases. By repeating the draw and adjustment process over multiple iterations, I generated a frequency distribution of adjusted results, from which I obtained a point estimate and simulation interval. These methods were applied without access to the primary record-level dataset. RESULTS: The conventional estimates of effect associating alachlor and glyphosate exposure with cancer incidence were likely biased away from the null and understated the uncertainty by quantifying only random error. For example, the conventional p-value for a test of trend in the alachlor study equaled 0.02, whereas fewer than 20% of the bias analysis iterations yielded a p-value of 0.02 or lower. Similarly, the conventional fully-adjusted result associating glyphosate exposure with multiple myeloma equaled 2.6 with 95% confidence interval of 0.7 to 9.4. The frequency distribution generated by the bias analysis yielded a median hazard ratio equal to 1.5 with 95% simulation interval of 0.4 to 8.9, which was 66% wider than the conventional interval. CONCLUSION: Bias analysis provides a more complete picture of true uncertainty than conventional frequentist statistical analysis accompanied by a qualitative description of study limitations. The latter approach is likely to lead to overconfidence regarding the potential for causal associations, whereas the former safeguards against such overinterpretations. Furthermore, such analyses, once programmed, allow rapid implementation of alternative assignments of probability distributions to the bias parameters, so elevate the plane of discussion regarding study bias from characterizing studies as ""valid"" or ""invalid"" to a critical and quantitative discussion of sources of uncertainty.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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majority of described cases, animal somatic cells round up as they get in mitosis. When cells are in a dense tissue, like an epithelium or a tumor, they are able to deform their neighbors to achieve a nearly perfect spherical shape. Several studies have investigated the molecular and structural changes related to mitotic rounding, but the function of this drastic change in shape is still unknown. Many cultured animal cells display a similar mitotic rounding behavior, interphase cells being often only a few microns high (typically 5 to 7  $\mu\text{m}$ ), while spherical mitotic cells can reach up to 20  $\mu\text{m}$  above the culture substrate. We developed a device to precisely control the distance between two surfaces, one bearing cultured cells and the other being made of a material of controlled stiffness. Cells were able to deform ceilings of up to a few kPa while rounding up, which is a typical tissue stiffness. But for harder ceiling (above 10 kPa), they were prevented from rounding and displayed spindle orientation and spindle assembly defects. Using hard ceilings, we precisely varied the spacing. When the ceiling was at 10  $\mu\text{m}$ , spindle orientation was lost but division was normal. Leaving even less place for cell rounding lead to formation of abnormal spindles: normal bipolar mitotic spindles would first form but spindle poles would eventually break before all chromosome had congressed, leading to multipolar spindles, mitotic catastrophe and eventually death of cells attempting to divide. We then tried to understand why mitotic spindle assembly is affected by space limitation. Studying in more details chromosome congression in mitotic cell prevented from rounding, we observed that chromosome capture and bi-orientation was strongly affected, leading to chromosomes detaching from the metaphase plate, eventually forming ectopic poles. A model for efficient kinetochore bi-orientation was recently proposed by A. Khodjakov and A. Mogilner, stating that initial chromosome organization in a 'stable star' conformation was essential. Lack of space would thus prevent such a spatial organization of prometaphase chromosomes, leading to mono-oriented kinetochores, or even synthetic attachments. When the delay in kinetochore capture was too long, unattached kinetochores would nucleate their own microtubule fibers, eventually leading to formation of ectopic spindle poles. These results lead us to propose the following working model: mitotic cell rounding would allow cells to push their neighbors and thus to protect the space in which the mitotic spindle is assembled, in order to accurately segregate their chromosomes. In addition, our assay might allow us to discover the precise mechanism by which cells are able to round up when confined by a soft material. We could show that affecting cell rounding mechanism would induce death of cells attempting to divide under a soft material, while either control cells under similar constrain, or cells treated but not confined would divide normally. Cancer cells might be even more sensitive than normal cells to defects in rounding as they often have more chromosomes and are growing in a stiffer environment, suggesting that targeting mitotic cell rounding could be a potent anti-tumor

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However, it remains unclear whether lrECM-dependent cell rounding and global histone deacetylation are indeed part of a common physical-biochemical pathway. Using 3D cultures as well as nonadhesive and micropatterned substrata, here we showed that the cell 'rounding' caused by lrECM was sufficient to induce deacetylation of histones H3 and H4 in the absence of biochemical cues. Microarray and confocal analysis demonstrated that this deacetylation in 3D culture is associated with a global increase in chromatin condensation and a reduction in gene expression. Whereas cells cultured on plastic substrata formed prominent stress fibers, cells grown in 3D lrECM or on micropatterns lacked these structures. Disruption of the actin cytoskeleton with cytochalasin D phenocopied the lrECM-induced cell rounding and histone deacetylation. These results reveal a novel link between ECM-controlled cell shape and chromatin structure and suggest that this link is mediated by changes in the actin cytoskeleton."

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tumor-targeting and antitumor activities. The purpose of this study was to investigate the modulation of the tumor-targeting efficiency of *Salmonella enterica* serovar choleraesuis by modifying the immune response to these bacteria by coating them with poly(allylamine hydrochloride) (PAH), designated PAH-S.C. To evaluate this modulation, we used naïve mice and mice immunized with *Salmonella* to study the role of the preexisting immune response to the antitumor activity of PAH-S.C. When anti-*Salmonella* antibodies were present, the invasion activity, cytotoxicity, and gene transfer of *Salmonella* was significantly decreased, both in vitro and in vivo. Treatment with PAH-S.C. resulted in delayed tumor growth and enhanced survival in immunized mice. Furthermore, immunohistochemical studies of the tumors revealed the infiltration of neutrophils and macrophages in immunized mice treated with PAH-S.C. These results indicate that *Salmonella* encapsulation effectively circumvented the *Salmonella*-specific immune response. What's new? *Salmonella* bacteria could make a good tool for delivering anti-tumor treatments, if it can get past the body's immune defenses. The bacteria, which can replicate under anaerobic conditions, preferentially multiply in tumors, where they can bring down the cancer from within, but the process grinds to a halt when the body starts churning out antibodies to round up and eliminate the *Salmonella*. The authors figured out how to envelop the bacteria with a polymer coating and disguise it from antibodies lurking in the bloodstream, ready to destroy it. In mice, the shielded bacteria evaded immune response and still targeted the tumor, plus showing lower toxicity to the host, suggesting that polymer coated *Salmonella* could be a very promising avenue for treatment. © 2012

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aminomethylphosphonic acid (AMPA), are analogs to glycine, thus they may inhibit serine hydroxymethyltransferase to decrease intracellular glycine synthesis. In this study, we found that glyphosate and AMPA inhibited cell growth in eight human cancer cell lines but not in two immortalized human normal prostatic epithelial cell lines. AMPA arrested C4-2B and PC-3 cancer cells in the G1/G0 phase and inhibited entry into the S phase of the cell cycle. AMPA also promoted apoptosis in C4-2B and PC-3 cancer cell lines. AMPA upregulated p53 and p21 protein levels as well as procaspase 9 protein levels in C4-2B cells, whereas it downregulated cyclin D3 protein levels. AMPA also activated caspase 3 and induced cleavage of poly (adenosine diphosphate [ADP]-ribose) polymerase. This study provides the first evidence that glyphosate and AMPA can inhibit proliferation and promote apoptosis of cancer cells but not normal cells, suggesting that they have potentials to be developed into a new anticancer

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Bisphosphonates are potent inhibitors of bone resorption. In vitro studies show that zoledronic acid inhibits prostate cancer cell growth by activating apoptosis. We investigated whether zoledronic acid also inhibits prostate cancer cell growth by autophagy (type II programmed cell death). MATERIALS AND METHODS: We investigated the induction of autophagy in the PC-3, DU-145, LNCaP and CRW22Rv1 cell lines upon zoledronic acid treatment. LC3-II protein formation was detected by Western blot. LC3-II incorporation into autophagosomes was detected by immunofluorescence staining. Acidic organelle formation was detected by acridine orange staining. Rescue experiments using an apoptosis inhibitor and/or an autophagy inhibitor were performed by MTT assay. RESULTS: Autophagy induction was detected by formation of the LC3-II protein after exposure to 100  $\mu$ M zoledronic acid. LC3-II and caspase-3 processing was detected 6 days after treatment. Acidic organelles were detectable by acridine orange staining and immunofluorescence showed round-up and condensed staining of LC3-II, suggesting autophagosome formation in the cytoplasm during autophagic cell death. Cell growth was rescued only by administering an apoptosis and autophagy inhibitor during zoledronic acid treatment, indicating that zoledronic acid induces prostate cancer death by apoptotic and autophagic cell death. CONCLUSIONS: To our knowledge we report the first study showing that zoledronic acid markedly inhibits human prostate cancer cell growth through autophagic cell death. Zoledronic acid shows its anticancer activity via apoptosis and autophagy. These findings can potentially contribute to the beneficial use of zoledronic acid for prostate cancer

treatment.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2000", "Lin, N., Garry, V. F.", "In vitro studies of cellular and molecular developmental toxicity of adjuvants, herbicides, and fungicides commonly used in Red River Valley, Minnesota", "Journal of toxicology and environmental health. Part A", "60(6):423-39", "f5b3ac75-0227-496c-b7d3-d62c697b6c57", "", "Recent epidemiologic studies showed increased frequency of birth defects in pesticide applicators and general population of the Red River Valley, Minnesota. These studies further indicated that this crop growing area used more chlorophenoxy herbicides and fungicides than elsewhere in Minnesota. Based on frequency of use and known biology, certain herbicides, pesticide additives, fungicides, and

mycotoxins are suspect agents. To define whether these agents affect developmental endpoints in vitro, 16 selected agrochemicals were examined using the MCF-7 breast cancer cell line. In the flow cytometric assay, cell proliferation in this estrogen-responsive cell line indicates xenobiotic-mediated estrogenic effects. Cell viability, morphology, ploidy, and apoptosis were incorporated in this assay. Data showed that the adjuvants X-77 and Activate Plus induced significant cell proliferation at 0.1 and 1 microg/ml. The commercial-grade herbicides 2,4-D LV4 and 2,4-D amine induced cell proliferation at 1 and 10 microg/ml. The reagent-grade 2,4-D products failed to induce proliferation over the same concentration range, suggesting that other ingredients in the commercial products, presumably adjuvants, could be a factor in these results. The fungicides triphenyltin and mancozeb induced apoptosis at concentrations of 4.1 microg/ml ( $10^{-5}$  M) and 50 microg/ml, respectively. Triphenyltin also induced aneuploidy (C2/M arrest) at 0.41 microg/ml ( $10^{-6}$  M). Data provide a mechanistic step to understanding human reproductive and developmental effects in populations exposed to these agrochemicals, and initiative to focusing limited resources for future in vivo animal developmental toxicity studies.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2010", "Lin, Y. C., Lin, J. F., Tsai, T. F., Chen, H. E., Chou, K. Y., Hwang, T. I. S., Kong, S.", "Zoledronic acid induces autophagic cell death in human prostate cancer cells", "", "7:236", "dcc9fa64-affb-4a97-bd7b-853aa52aac42", "", "Objective: Bisphosphonates are potent inhibitors of bone resorption frequently used for breast cancer and myeloma-induced bone disease. Zoledronic acid (ZA) has been recently shown to also reduce skeletal morbidity from prostate cancer. In vitro studies also showed that ZA inhibit prostate cancer cell growth by activating caspase cascade which leading to apoptosis cell death. In this study, we investigate whether ZA also inhibit prostate cancer cell growth by type-II programmed cell death, autophagy. Material and Methods: MTT assay was introduced to investigate the biological effects of ZA on PC-3 and DU-145, androgen-independent human prostate cancer cell lines, as well as LNCaP and CRW22Rv1, androgen-sensitive cell lines. The formation of LC3-II protein, a marker protein involved in the formation of autophagosome during autophagic cell death, was detected by Western blot. Formation of acidic organelles was detected by acridine orange staining. LC3-II incorporation into autophagosome was detected by Immunofluorescent (IF) staining. Results: ZA exhibited dose and time-dependent growth inhibition on four human prostate cancer cell lines investigated. Apoptosis was demonstrated by caspase-3 activation. Autophagic cell death was detected by the formation of LC3-II protein as early as 24 hours exposure to 100 nM of ZA. Acidic organelles were detectable by acridine orange staining and IF showed round-up and condensed staining of LC3-II, suggesting the formation of autophagosome in the cytoplasm during autophagic cell death. The rescue of cell growth occurred only by administration of both apoptosis and autophagy inhibitor during ZA treatment suggesting ZA induces prostate cancer death by either apoptosis or autophagic cell death. Conclusion: This is the first study showed that ZA markedly inhibit human prostate cancer cells growth through autophagic cell death. ZA can exhibit its anti-cancer activity via both apoptosis and autophagy. These findings could potentially contribute to the beneficial effect of ZA in prostate cancer treatments.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Liu, G., Peng, Z., Lan, T., Xu, X., Huang, G., Yu, S., Liu, G., Li, J.", "[Health risk assessment on pesticide residues in drinking water in Shenzhen]", "Wei sheng yan jiu = Journal of hygiene

research", "44(2):264-9", "ccd9b5b3-4376-4838-98f2-589fe2d263c7", "", "OBJECTIVE: To conduct a health risk assessment of pesticide residues and its annual trend analysis in drinking water in Shenzhen City. METHODS: The water quality monitoring data of product water, pipe water and secondary supply water during from 2011 to 2013 were collected and analyzed. The risk evaluation models recommended by the U. S. Environmental Protection Agency (USEPA) were employed to perform health risk assessments for children and adults on the 12 non-carcinogenic materials (namely, heptachlor, pentachlorophenol, hexachlorocyclohexane, hexachlorobenzene, DDT, malathion, glyphosate, dimethoate, bentazone, atrazine, chlorothalonil, furadan). Results The results of the analysis for water quality from 84 factory samples, 11 peripheral samples and one secondary supply water sample showed that all of the measured indicators in the above mentioned water samples met the National Health Standards (GB 5749-2006) published by Ministry of Health of the People's Republic of China. The adults and children's health indices (HIs) of the 12 non-carcinogenic materials were greater than 1 (2.323 - 6.312). Dimethoate in factory and peripheral water samples posed the largest risks of harm among the non-carcinogenic pollutants measured. And its HIi were also greater than 1 (1.995 - 5.094) and followed by hexachlorobenzene and heptachlor. Annual rising trend on health risk of the 12 pesticide residues indicated that their HIT on adults was  $2323.18 \times 10^{-3}$  in 2011,  $2340.18 \times 10^{-3}$  in 2012 and  $2431.97 \times 10^{-3}$  in 2013, and on children  $2965.07 \times 10^{-3}$  in 2011,  $2986.77 \times 10^{-3}$  in 2012 and  $3103.93 \times 10^{-3}$  in 2013, respectively. This study also suggested that the average risk of peripheral water samples (HIT was equal to  $2619.64 \times 10^{-3}$ ) was greater than that of factory samples (HIT was same as  $2366.92 \times 10^{-3}$ ), and more children's health risk than adults' risk. CONCLUSION: Health risks of pesticide residues in drinking water in Shenzhen have exceeded the threshold value and dimethoate was the main hazard and more children's health risk than adults' risk. Furthermore, there was an annual rising slowly trend on health risks of pesticide residues in drinking water.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2009", "Lorimer, I. A. J., Gray, D. A., Baldwin, M.", "Protein kinase C  $\iota$  as a target for glioblastoma therapy", "", "8(12)", "5447e690-8ca3-4f2f-b4b8-976dd2f95ddl", "", "In spite of advances in surgery, radiation and chemotherapy, glioblastoma is still one of the deadliest forms of cancer. Two key features of the malignant nature of glioblastoma are its abnormal proliferation and its ability to invade both locally and to distant sites within the central nervous system. The phosphoinositide 3-kinase pathway is frequently activated by oncogenic mutations in glioblastoma, leading to activation of multiple downstream signaling molecules including protein kinase C  $\iota$  (PKC $\iota$ ). Stable suppression of PKC $\iota$  in glioblastoma cells with a short hairpin RNA caused a significant decrease in the proliferation of glioblastoma cells along with increased actin stress fiber formation and decreased cell motility and invasion. Live cell imaging was used to further assess the role of PKC $\iota$  in glioblastoma cell motility and proliferation. While control glioblastoma cells form a coordinated leading edge lamellipodia and migrate substantial distances, cells stably depleted of PKC $\iota$  show a loss of the ability to coordinate the formation of a functional leading edge lamellipodia and instead generate projections from all sides of the cell. These cells are therefore unable to move in a coordinated fashion. In addition live cell imaging showed that while glioblastoma cells round up and initiate mitosis, they are significantly impaired in their ability to complete mitosis. These effects on motility and mitosis were also seen when PKC $\iota$

activity was inhibited with a myristoylated pseudosubstrate peptide. PKC $\delta$  is therefore a promising new therapeutic target for glioblastoma.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Ma, J., Li, X.", "Alteration in the cytokine levels and histopathological damage in common carp induced by glyphosate", "Chemosphere", "128:293-8", "bd07292f-7b6b-4d7b-8935-862d3b1c510d", "", "Glyphosate is one of the most frequently used herbicides, and it has been demonstrated to generate a series of toxicological problems in animals and humans. However, relatively little is known about the effects of glyphosate on the immune system of fish. In the present study, the acute toxicity of glyphosate on common carp was first determined; then, the contents of interferon-gamma (IFN-gamma), interleukin-1beta (IL-1beta), and tumor necrosis factor -alpha (TNF-alpha) and histopathological alterations in the liver, kidneys, and spleen of common carp exposed to 52.08 or 104.15 mg L<sup>-1</sup> of glyphosate for 168 h were also determined and evaluated. The results of the acute toxicity tests showed that the 96 h LC50 of glyphosate for common carp was 520.77 mg L<sup>-1</sup>. Moreover, sub-acute exposure of glyphosate altered the contents of IFN-gamma, IL-1beta, and TNF-alpha in fish immune organs. For example, there was a remarkable increase in the IFN-gamma content in the kidneys, while there was a decrease in the liver and spleen. The IL-1beta content increased in liver and kidneys, but it decreased in the spleen, and TNF-alpha mainly increased in the fish liver, kidneys, and spleen. In addition, glyphosate-exposure also caused remarkable histopathological damage in the fish liver, kidneys, and spleen. These results suggest that glyphosate-caused cytokine alterations may result in an immune suppression or excessive activation in the treated common carp as well as may cause immune dysfunction or reduced immunity. In conclusion, glyphosate has immunotoxic effects on common carp.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2009", "Makowski, M., PoÅ, aÅ†, I., PertyÅ„ski, T.", "Oestrogen receptor alpha polymorphisms in women with breast cancer and their clinical significance", "", "13(1):40-44", "e57432c8-c87d-4980-a74e-5a37752a5aee", "", "Oestrogen receptors have a wide spectrum of activity. Their prevalence in many organs suggests possible clinical ramifications. The tests that have been carried out until now do not determine whether prevalence of oestrogen receptor polymorphism has clinical significance and whether it can be put into everyday practice, especially with diagnostics and treatment of breast cancer. In this review we present a roundup of information about the influence of oestrogen receptor polymorphism on breast cancer occurrence and its clinical ramifications.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2008", "Malatesta, M., Perdoni, F., Santin, G., Battistelli, S., Muller, S., Biggiogera, M.", "Hepatoma tissue culture (HTC) cells as a model for investigating the effects of low concentrations of herbicide on cell structure and function", "Toxicology in vitro : an international journal published in association with BIBRA", "22(8):1853-60", "42b541ca-fc78-4b32-a78a-1ca0570becd9", "", "Previous studies on mice fed genetically modified (GM) soybean demonstrated modifications of the mitochondrial functions and of the transcription/splicing pathways in hepatocytes. The cause(s) of these alterations could not be conclusively established but, since the GM soybean used is tolerant to glyphosate and was treated with the glyphosate-containing herbicide Roundup , the possibility exists that the effects observed may be due to herbicide residues. In order

to verify this hypothesis, we treated HTC cells with 1-10mM Roundup and analysed cellular features by flow cytometry, fluorescence and electron microscopy. Under these experimental conditions, the death rate and the general morphology of HTC cells were not affected, as well as most of the cytoplasmic organelles. However, in HTC-treated cells, lysosome density increased and mitochondrial membranes modified indicating a decline in the respiratory activity. Moreover, nuclei underwent morpho-functional modifications suggestive of a decreased transcriptional/splicing activity. Although we cannot exclude that other factors than the presence of the herbicide residues could be responsible for the cellular modifications described in GM-fed mice, the concordance of the effects induced by low concentrations of Roundup on HTC cells suggests that the presence of Roundup residues could be one of the factors interfering with multiple metabolic pathways.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2013", "Malecot, M., Guevel, B., Pineau, C., Holbech, B. F., Bormans, M., Wiegand, C.", "Specific proteomic response of *Unio pictorum* mussel to a mixture of glyphosate and microcystin-LR", "Journal of proteome research", "12(11):5281-92", "366f07d5-b6e2-4094-b3c4-0c086c798d71", "", "Cyanobacterial toxins and pesticides regularly impact freshwaters. Microcystin-LR is one of the most toxic and common cyanobacterial toxins whereas glyphosate is the active ingredient of a widely use herbicide. As filter feeders, freshwater mussels are particularly exposed. Like many native bivalve species, *Unio pictorum* suffers from a continuous decline in Europe. In order to get a deeper insight of its response to contaminants, *U. pictorum* was exposed to either 10 mug L<sup>-1</sup> of microcystin-LR or 10 mug L<sup>-1</sup> of glyphosate or a mixture of both. Proteins of the digestive glands were extracted and analyzed by DIGE. Gel analysis revealed 103 spots with statistical variations, and the response seems to be less toward glyphosate than to microcystin-LR. Specific spots have variations only when exposed to the mixture, showing that there is an interaction of both contaminants in the responses triggered. The proteins of 30 spots have been identified. They belong mostly to the cytoskeleton family, but proteins of the oxidative pathway, detoxification, and energetic metabolism were affected either by glyphosate or microcystin-LR or by the mixture. These results demonstrate the importance to study contaminants at low concentrations representative of those found in the field and that multicontaminations can lead to different response pathways.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2009", "Manas, F., Peralta, L., Raviolo, J., Garcia Ovando, H., Weyers, A., Ugnia, L., Gonzalez Cid, M., Larripa, I., Gorla, N.", "Genotoxicity of AMPA, the environmental metabolite of glyphosate, assessed by the Comet assay and cytogenetic tests", "Ecotoxicology and environmental safety", "72(3):834-7", "7d0b94dc-6397-44b6-a43f-1c364f691009", "", "Formulations containing glyphosate are the most widely used herbicides in the world. AMPA is the major environmental breakdown product of glyphosate. The purpose of this study is to evaluate the in vitro genotoxicity of AMPA using the Comet assay in Hep-2 cells after 4h of incubation and the chromosome aberration (CA) test in human lymphocytes after 48h of exposition. Potential in vivo genotoxicity was evaluated through the micronucleus test in mice. In the Comet assay, the level of DNA damage in exposed cells at 2.5-7.5mM showed a significant increase compared with the control group. In human lymphocytes we found statistically significant clastogenic effect AMPA at 1.8mM compared with the control group. In vivo, the micronucleus test rendered significant statistical increases at 200-400mg/kg. AMPA was genotoxic in the three performed tests. Very scarce data are

available about AMPA potential genotoxicity.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2011", "Mann, H. F., Vencovsky, J.", "Clinical trials roundup in idiopathic inflammatory myopathies", "Current opinion in rheumatology", "23(6):605-11", "df0fce58-fa9d-454f-b4c4-9388d955b0ab", "", "PURPOSE OF REVIEW: To review recent advances in the treatment of idiopathic inflammatory myopathies (IIMs) with emphasis on new biological agents and on some less commonly used immunosuppressive drugs. RECENT FINDINGS: Double-blinded comparison of oral high-dose pulse dexamethasone with standard high daily prednisolone doses showed similar efficacy in the composite score, significantly longer median time to relapse with prednisolone and fewer side effects with dexamethasone treatment. Use of intravenous immunoglobulins (IVIGs) in IIMs is associated with variable results; however, recent retrospective evaluation of IVIGs administration to steroid-resistant patients with esophageal involvement showed good effect. Whereas smaller open studies with rituximab reported a very good efficacy, even in notoriously difficult-to-treat anti-signal recognition particle-positive cases, the double-blind trial has not reached the primary endpoint. Studies with TNF neutralization are reporting results ranging from only a modest or no effect to a promising outcome in the most recent trial with etanercept. Pilot studies suggest efficacy of alemtuzumab in inclusion body myositis and allogeneic mesenchymal stem cell transplantation in polymyositis/dermatomyositis. SUMMARY: Unmet need for efficacious therapy in IIMs exists and therefore a coordinated effort is necessary to properly evaluate various new classical and biological agents.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2014", "Mantovani, A., Fucic, A.", "Puberty dysregulation and increased risk of disease in adult life: Possible modes of action", "", "44:15-22", "7b35b716-8b60-45c5-b28d-dbcef45d99fd", "", "Puberty is the developmental window when the final maturation of body systems is orchestrated by hormones; lifelong sex-related differences and capacity to interact with the environment are defined during this life stage. Increased incidence in a number of chronic, multifactorial diseases could be related to environmental exposures during puberty: however, insight on the susceptibility of the peripubertal period is still limited. The estrogen/androgen balance is a crucial axis in harmonizing the whole pubertal development, pointing out the significance of exposures to endocrine disruptors. Besides the reproductive system, endocrine-related perturbations may affect the maturation of skeleton, adipose tissues, brain, immune system, as well as cancer predisposition. Thus, risk assessment of environmental stressors should duly consider specific aspects of the pubertal window. Besides endocrine-related mechanisms, suggested research priorities include signaling molecules (e.g., kisspeptins, dopamine) as xenobiotic targets and disturbances of specific pubertal methylation processes potentially involved in neurobehavioral disorders and cancer risk in adulthood. Â© 2013 Elsevier Inc.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2004", "Marc, J., Mulner-Lorillon, O., Belle, R.", "Glyphosate-based pesticides affect cell cycle regulation", "Biology of the cell / under the auspices of the European Cell Biology Organization", "96(3):245-9", "4336cfe0-578c-41a5-a5d4-22be33db13a5", "", "Cell-cycle dysregulation is a hallmark of tumor cells and human cancers. Failure in the cell-cycle checkpoints leads to genomic instability and subsequent development of cancers from the initial affected cell. A worldwide used product Roundup 3plus, based on glyphosate as the active herbicide, was suggested to be of human health concern since it induced cell cycle dysfunction as

judged from analysis of the first cell division of sea urchin embryos, a recognized model for cell cycle studies. Several glyphosate-based pesticides from different manufacturers were assayed in comparison with Roundup 3plus for their ability to interfere with the cell cycle regulation. All the tested products, Amega, Cargly, Cosmic, and Roundup Biovert induced cell cycle dysfunction. The threshold concentration for induction of cell cycle dysfunction was evaluated for each product and suggests high risk by inhalation for people in the vicinity of the pesticide handling sprayed at 500 to 4000 times higher dose than the cell-cycle adverse concentration.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2013", "Marrelli, M., Tudisco, R., Mastellone, V., Conforti, F.", "A comparative study of phytochemical composition of genetically and non-genetically modified soybean (*Glycine max* L.) and evaluation of antitumor activity", "Natural product research", "27(6):574-8", "ec736012-8ab3-466e-9b8d-71981dad4761", "", "Colon cancer is one of the major causes of cancer mortality worldwide. The analysed feeds, containing non-genetically modified (GM) soybean and Roundup Ready soybean, showed a different polyphenolic content and lipophilic composition. Non-GM soybean extract possessed twice the polyphenolic content of GM soybean and the highest number of sterols. Among them, gamma-sitosterol was found to be the major constituent. Methanolic extract of non-GM soybean extract was more potent than GM soybean extract against colon carcinoma cell line LoVo using MTT assay, while the second one showed a slightly higher anti-inflammatory activity. The findings add to epidemiological evidence for the therapeutic effects of soy foods in colorectal carcinoma.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "1995", "Marushige, Y., Marushige, K.", "Disappearance of ubiquitinated histone H2A during chromatin condensation in TGF beta 1-induced apoptosis", "Anticancer research", "15(2):267-72", "341cf6e0-4be0-4b11-80cb-201b0af8eed6", "", "Chromatin condensation during apoptosis induced by TGF beta 1 in T24 glioma and 476-16 trigeminal neurinoma (Schwannoma) cells was examined and compared with that occurring during mitosis. Apoptotic (round-up) cells were selectively detached from the culture surface by a mechanical shock. Their histones were analysed in comparison with those obtained from TGF beta 1-treated cells remaining attached to the culture surface, from control cells not treated with TGF beta 1 and from metaphase cells. While mitosis-specific hyperphosphorylation of histones H1 and phosphorylation of histone H3 was not observed in apoptotic cells, apoptotic chromatin lacked ubiquitinated histone H2A (histone uH2A) as did metaphase chromosomes. The cellular level of free ubiquitin and the overall pattern of ubiquitin-conjugated proteins were, however, found to remain unaltered in apoptotic cells, suggesting that the ubiquitin conjugating machinery for histone H2A may be specifically perturbed during the chromatin condensation occurring in apoptosis.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2010", "Mendoza, J., Agus, B., Lanyi, V. F.", "An unusual etiology of acute sero-negative polyarthrititis: A case report", "", "2(9):S13", "beae1220-a174-4491-bf89-71c44e8aa9f2", "", "Patients or Programs: The patient is a 49-year-old man admitted to acute rehabilitation facility with severe acute polyarthrititis. Program Description: Diagnosis of psoriatic arthritis was made via skin biopsy of large virulent appearing patches in addition to diffuse joint pain and swelling. On initial presentation, patient had psoriatic rash encompassing his entire body. He was extremely limited in his ability to walk and perform most activities of

daily living (ADL) due to pain and stiffness in his extremities and his back. Pain typically kept patient up throughout the night. He received steroids before admission with limited therapeutic benefit. Patient was started on anti-tumor necrosis factor (TNF) drug and began to improve. Patient received care from a multidisciplinary team directed at pain control, improving range of motion and ambulation, and restoring overall ability to perform ADLs at premorbid capacity. Of interest, a recent report from the American College of Rheumatology's Annual Meeting (October 2009) suggested insecticides may trigger autoimmune disease. Patient reported that 2 years prior he developed a rash after use of "Round-Up" (insecticide). The following year, patient again developed a rash after use of "Round-Up," which escalated to rash seen on presentation. Setting: Tertiary care setting. Results: Once anti-TNF therapy began, patient made great strides in rehabilitation as he was having less pain in the morning and was sleeping through the night. His range of motion significantly improved as did his joint swelling. At discharge he was ambulating and performing ADLs at modified independent level. Discussion: With proper medical management and aggressive rehabilitation, patients with psoriatic arthritis may see great improvement. Our case made us aware of the possibility that insecticides may trigger autoimmune disease. This knowledge may benefit future patients as earlier treatment may lead to improved long-term outcome. Conclusions: An integrated rehabilitation program for a patient presenting with psoriatic arthritis can facilitate a return to functional independence.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2014", "Mesnage, R., Defarge, N., Spiroux de Vendomois, J., Seralini, G. E.", "Major pesticides are more toxic to human cells than their declared active principles", "BioMed research international", "2014:179691", "dd3f1b78-d7c1-451b-ab37-b7beb5d7cfaf", "", "Pesticides are used throughout the world as mixtures called formulations. They contain adjuvants, which are often kept confidential and are called inerts by the manufacturing companies, plus a declared active principle, which is usually tested alone. We tested the toxicity of 9 pesticides, comparing active principles and their formulations, on three human cell lines (HepG2, HEK293, and JEG3). Glyphosate, isoproturon, fluroxypyr, pirimicarb, imidacloprid, acetamiprid, tebuconazole, epoxiconazole, and prochloraz constitute, respectively, the active principles of 3 major herbicides, 3 insecticides, and 3 fungicides. We measured mitochondrial activities, membrane degradations, and caspases 3/7 activities. Fungicides were the most toxic from concentrations 300-600 times lower than agricultural dilutions, followed by herbicides and then insecticides, with very similar profiles in all cell types. Despite its relatively benign reputation, Roundup was among the most toxic herbicides and insecticides tested. Most importantly, 8 formulations out of 9 were up to one thousand times more toxic than their active principles. Our results challenge the relevance of the acceptable daily intake for pesticides because this norm is calculated from the toxicity of the active principle alone. Chronic tests on pesticides may not reflect relevant environmental exposures if only one ingredient of these mixtures is tested alone.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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herbicides (GlyBH), including Roundup, are the most widely used pesticides worldwide. Their uses have increased exponentially since their introduction on the market. Residue levels in food or water, as well as human exposures, are escalating. We have reviewed the toxic effects of GlyBH measured below regulatory limits by evaluating the published literature and regulatory reports. We reveal a coherent body of evidence indicating that GlyBH could be toxic below the regulatory lowest observed adverse effect level for chronic toxic effects. It includes teratogenic, tumorigenic and hepatorenal effects. They could be explained by endocrine disruption and oxidative stress, causing metabolic alterations, depending on dose and exposure time. Some effects were detected in the range of the recommended acceptable daily intake. Toxic effects of commercial formulations can also be explained by GlyBH adjuvants, which have their own toxicity, but also enhance glyphosate toxicity. These challenge the assumption of safety of GlyBH at the levels at which they contaminate food and the environment, albeit these levels may fall below regulatory thresholds. Neurodevelopmental, reproductive, and transgenerational effects of GlyBH must be revisited, since a growing body of knowledge suggests the predominance of endocrine disrupting mechanisms caused by environmentally relevant levels of exposure.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Mettler, L., Alkatout, I.", "Surgical and imaging approach in diagnosis and therapy of uterine myomas", "", "37(1):22-34", "ffd002be-9471-42d4-977c-16e875bf702f", "", "With our catalogue of indications in the areas of gynec-endoscopic surgery, published in 2002 (1), we reveal the broad application of endoscopic surgery at the beginning of this millennium. Particularly the diagnosis and treatment of uterine fibroids have been a stimulus for the development of operative laparoscopic surgeries in the early 1970ies till today (2). Three-dimensional vision, robotic instruments and systems, such as the da Vinci® Surgical System from Intuitive Surgical Inc., round up today the picture of endoscopic surgery. The advantages of endoscopic surgery over open surgery (more precision, less trauma, less post operative pain, shorter hospital stays and a faster recovery period) are becoming more accepted. The present health care systems and hospital administrations understand the challenges of imaging in surgery, particularly in endoscopic surgery.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2008", "Mink, P. J., Adami, H. O., Trichopoulos, D., Britton, N. L., Mandel, J. S.", "Pesticides and prostate cancer: A review of epidemiologic studies with specific agricultural exposure information", "", "17(2):97-110", "3e9b0190-16a1-4d4f-8a06-21cc749fb741", "", "Prostate cancer is the most commonly diagnosed cancer in US men, and the second most commonly diagnosed cancer among men worldwide. Although pesticides have been implicated in studies of prostate cancer among farmers, meta-analyses have found heterogeneity across studies, and a number of exposures and lifestyle factors may be unique to farmers. The purpose of this paper is to review the epidemiologic literature to evaluate the hypothesis that agricultural exposure to pesticides is causally associated with prostate cancer risk. We analyzed the eight cohort studies and five case-control studies that quantified and/or evaluated agricultural exposure to particular pesticide classes or chemicals. Despite sporadic positive findings, these studies did not show consistently increased risks to support a causal association between agricultural pesticide use and prostate cancer. Studies using an 'external' comparison group must be interpreted in the context of confounding by differences in prostate-specific antigen screening intensity. Furthermore, most studies did not adjust for potential confounders

other than age and time period. It is clearly not possible to exonerate any particular pesticide as a putative cause of prostate cancer - to do so would require an inverse empirical association with an upper confidence limit below the null value. Existing evidence does not point to any pesticide as satisfying widely used guidelines for establishing causation: a strong, exposure-dependent and demonstrably unconfounded, unbiased association, documented in several studies.

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2011", "Mink, P. J., Mandel, J. S., Lundin, J. I., Scurman, B. K.", "Epidemiologic studies of glyphosate and non-cancer health outcomes: a review", "Regulatory toxicology and pharmacology : RTP", "61(2):172-84", "8ee20d46-04f1-4d0c-b4d7-bc6d60b97b6e", "", "The United States (US) Environmental Protection Agency (EPA) and other regulatory agencies around the world have registered glyphosate as a broad-spectrum herbicide for use on multiple food and non-food use crops. To examine potential health risks in humans, we searched and reviewed the literature to evaluate whether exposure to glyphosate is associated causally with non-cancer health risks in humans. We also reviewed biomonitoring studies of glyphosate to allow for a more comprehensive discussion of issues related to exposure assessment and misclassification. Cohort, case-control and cross-sectional studies on glyphosate and non-cancer outcomes evaluated a variety of endpoints, including non-cancer respiratory conditions, diabetes, myocardial infarction, reproductive and developmental outcomes, rheumatoid arthritis, thyroid disease, and Parkinson's disease. Our review found no evidence of a consistent pattern of positive associations indicating a causal relationship between any disease and exposure to glyphosate. Most reported associations were weak and not significantly different from 1.0. Because accurate exposure measurement is crucial for valid results, it is recommended that pesticide-specific exposure algorithms be developed and validated.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2012", "Mink, P. J., Mandel, J. S., Scurman, B. K., Lundin, J. I.", "Epidemiologic studies of glyphosate and cancer: a review", "Regulatory toxicology and pharmacology : RTP", "63(3):440-52", "84ba15c1-4ee2-40d2-afcb-b9756e18c6ae", "", "The United States Environmental Protection Agency and other regulatory agencies around the world have registered glyphosate as a broad-spectrum herbicide for use on multiple food and non-food use crops. Glyphosate is widely considered by regulatory authorities and scientific bodies to have no carcinogenic potential, based primarily on results of carcinogenicity studies of rats and mice. To examine potential cancer risks in humans, we reviewed the epidemiologic literature to evaluate whether exposure to glyphosate is associated causally with cancer risk in humans. We also reviewed relevant methodological and biomonitoring studies of glyphosate. Seven cohort studies and fourteen case-control studies examined the association between glyphosate and one or more cancer outcomes. Our review found no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate. Data from biomonitoring studies underscore the importance of exposure assessment in epidemiologic studies, and indicate that studies should incorporate not only duration and frequency of pesticide use, but also type of pesticide formulation. Because generic exposure assessments likely lead to exposure misclassification, it is recommended that exposure algorithms be validated with biomonitoring data.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2012", "Monnier, L., Schlienger, J. L., Colette, C.", "Alert in genetically modified plants: Much ado about nothing or almost nothing?", "", "6(5):447-450", "0a741225-8d57-41f5-8550-19700d13c89d", "", "By comparing the effects of long-term diets enriched with two strains of maize (a Roundup-tolerant genetically strain vs. a non-transgenic type) French researchers have recently reported that Sprague-Dawley rats were at increased risk for deaths and tumors when submitted to feeding with the genetically modified plant. A more accurate analysis of the results seems to indicate that these adverse events were mainly observed in females. In males, the results are somewhat surprising since death rates were lower in the animals that had received the transgenic maize than in those that had been fed with the non-transgenic type. Such results sound to be profoundly discordant and controversial when compared with those previously published in the literature. Several remarks can be made. First it must be noted that the results were widely broadcasted by the medias before any reliable analysis by scientific experts of national or international Food Safety Authorities. Secondly there arises the question as to know why and how this study was really conducted. For instance the methodology (small sample size and controversial statistical analysis) is rather poor for a study that has the pretentiousness to provide a global position statement against the use of genetically modified plants. As a consequence these results should be submitted to the careful peer view of independent experts who do not disclose any conflict of interest. Further trials might be required but the highly likely inability to reproduce such observations would strongly contribute to affect their credibility. At the present time, the reliability of the unsubstantiated alert alleged by this article is pending, and it is suggested to the authors that they meditate the famous Charles Darwin's aphorism: ""To kill an error is as good a service, and sometimes even better, than the establishing of a new truth or fact"". Â© 2012 - Elsevier Masson SAS - Tous droits r serv s.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2005", "Monroy, C. M., Cortes, A. C., Sicard, D. M., de Restrepo, H. G.", "[Cytotoxicity and genotoxicity of human cells exposed in vitro to glyphosate]", "Biomedica : revista del Instituto Nacional de Salud", "25(3):335-45", "b9df4cb1-3788-4db1-b026-a87baf5683b4", "", "INTRODUCTION: Glyphosate is a broad-spectrum non-selective herbicide, used to eliminate unwanted weeds in agricultural and forest settings. Herbicide action is achieved through inhibition of aromatic amino acid biosynthesis in plant cells. Since this is not a conserved mechanism between human and plant cells, glyphosate is considered to be a low health risk substance for humans. However, the occurrence of possible harmful side effects of glyphosate use is not well documented and controversial. Toxicity and genotoxicity studies indicate that glyphosate is not harmful, although several investigations suggest that it can alter various cellular processes in animals. Therefore this has potential as a health and environmental risk factor in areas where glyphosate is widely used. OBJECTIVES: The present study evaluated glyphosate cytotoxic and genotoxic effects in normal human cells (GM38) and human fibrosarcoma (HT1080) cells. MATERIALS AND METHODS: Acute and chronic cytotoxicity were determined through the exposure of cultured cells to graded concentrations of glyphosate, and cell viability analysis was performed with crystal violet and Trypan blue staining. Genotoxicity was determined using the comet assay and data significance was evaluated with Dunnet's test. RESULTS: For chronic cytotoxicity a dose-dependent effect was observed in both GM38 and HT1080 cells after treatment with 5.2-8.5 mM and 0.9-3.0 mM glyphosate, respectively. In the acute cytotoxicity study, GM38 cells exposed to 4.0-7.0 mM glyphosate and HT1080 cells exposed to 4.5-5.8 mM glyphosate, had cell viability counts higher than 80%. Genotoxic effects were evidenced in GM38 cells at glyphosate concentrations of 4.0-6.5 mM and in HT1080 cells at glyphosate concentrations of 4.75 - 5.75 mM. CONCLUSIONS: The levels of cytotoxicity and genotoxicity of glyphosate occurring in mammalian cells suggested that its mechanism of action is not limited to plant cells.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2011", "Morgensztern, D., Govindan, R.", "A roundup of recently published articles relevant to thoracic oncology", "Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer", "6(7):1295-7", "e380cbb9-6009-40e3-bf29-a70d08ba2544", "", "We selected six publications for the ""best of the month,"" published recently in peer-reviewed journals, covering a broad range of topics including second-hand smoking, intensive care unit admissions for patients with lung cancer, role of aspirin in preventing lung cancer, bleeding events in patients undergoing treatment with bevacizumab and requiring full anticoagulation, level of evidence used to support the National Comprehensive Cancer Network guidelines, and the use of prophylactic cranial irradiation in patient with locally advanced non-small cell lung cancer.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2011", "Morgensztern, D., Govindan, R.", "Best of the month: A round up of articles published in recent months", "Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer", "6(1):223-6", "585c0207-04f1-478d-ab6e-d064c5c505c4", "", "With the abundant number of articles published in lung cancer, it has become very difficult to stay updated. After a search through variety of medical journal for articles published between March and June 2010, we selected the studies considered to have the greatest relevance for oncologists involved in the treatment of lung cancer. The nine selected studies covered a broad range of topics including possible hormonal role in the development of lung adenocarcinoma, lung cancer in never smokers, stereotactic radiotherapy for early-stage lung cancer, prognostic role of pleural lavage cytology, neoadjuvant chemotherapy for operable lung cancer, maintenance erlotinib, use of erlotinib after gefitinib, comparison of the two epidermal growth factor receptor tyrosine kinase inhibitors, and risk of central nervous system relapse in patients treated with epidermal growth factor receptor tyrosine kinase inhibitors.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2014", "Morrison, R., Gardiner, C., Evidente, A., Kiss, R., Townley, H.", "Incorporation of ophiobolin a into novel chemoembolization particles for cancer cell treatment", "Pharmaceutical research", "31(10):2904-17", "0c1a98cd-538d-47ef-942f-82529b197448", "", "PURPOSE: To design and synthesize chemoembolization particles for the delivery of Ophiobolin A (OphA), a promising fungal-derived chemotherapeutic, directly at the tumour location. To investigate cell death mechanism of OphA on a Rhabdomyosarcoma cancer (RD) cell line. Rhabdomyosarcoma is the most common soft tissue sarcoma in children; with a 5-year survival rate of between 30 and 65%. METHODS: Multimodal chemoembolization particles were prepared by sintering mesoporous silica nanoparticles, prepared by the sol-gel method, onto the surface of polystyrene microspheres, prepared by suspension copolymerisation. The chemoembolization particles were subsequently loaded with OphA. The effects of OphA in vitro were characterised by flow cytometry and nanoparticle tracking analysis (NanoSight). RESULTS: High loading of OphA onto the chemoembolization particles was achieved. The subsequent release of OphA onto RD cells in culture showed a 70% reduction in cell viability. OphA caused RD cells to round up and their membrane to bleb and caused cell death via apoptosis. OphA caused both an increase in the number of microvesicles produced and an increase in DNA content within these microvesicles. CONCLUSIONS: The prepared chemoembolization particles showed good efficacy against RD cells in culture.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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labelled aniline feeding studies revealed that aniline is not a precursor of indoles in strain JA2. Further, production of indoles only in aniline-exposed cells suggests that aniline is an indoles stimulator. In addition, production of indoles depended on the presence of a carbon source, and production enhanced when carbon sources were added to the culture. Isotope labelled fumarate feeding identified, fumarate as the precursor of indole, indicating de novo synthesis of indoles. Glyphosate (shikimate pathway inhibitor) inhibited the indoles production, accumulation of tryptophan, IAA and IAld indicating that indoles synthesis in strain JA2 occurs via the de novo shikimate pathway. The up-regulation of anthranilate synthase gene and induction of anthranilate synthase activity correlated well with tryptophan production in strain JA2. Induction of tryptophan aminotransferase and tryptophan 2-monooxygenase activities corroborated well with IAA levels, suggesting that tryptophan catabolism occurs simultaneously in aniline exposed cells. Our study demonstrates that aniline (stress) stimulates tryptophan/indoles synthesis via the shikimate pathway by possibly modulating the metabolic pathway.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

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and epidemiological studies. It also examines the derivation of current human safety standards. We conclude that: (1) GBHs are the most heavily applied herbicide in the world and usage continues to rise; (2) Worldwide, GBHs often contaminate drinking water sources, precipitation, and air, especially in agricultural regions; (3) The half-life of glyphosate in water and soil is longer than previously recognized; (4) Glyphosate and its metabolites are widely present in the global soybean supply; (5) Human exposures to GBHs are rising; (6) Glyphosate is now authoritatively classified as a probable human carcinogen; (7) Regulatory estimates of tolerable daily intakes for glyphosate in the United States and European Union are based on outdated science. We offer a series of recommendations related to the need for new investments in epidemiological studies, biomonitoring, and toxicology studies that draw on the principles of endocrinology to determine whether the effects of GBHs are due to endocrine disrupting activities. We suggest that common commercial formulations of GBHs should be prioritized for inclusion in government-led toxicology testing programs such as the U.S. National Toxicology Program, as well as for biomonitoring as conducted by the U.S. Centers for Disease Control and

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Verlag.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2014", "Oh, J. S., Choi, K. H.", "Methemoglobinemia associated with metaflumizone poisoning", "Clinical toxicology (Philadelphia, Pa.)", "52(4):288-90", "0057d1c4-9999-424c-b2f2-d263881040e1", "", "CONTEXT: Metaflumizone is a voltage-dependent sodium channel blocker insecticide, which is

chemically similar to indoxacarb. Although indoxacarb poisoning is known as a cause of methemoglobinemia, the effect of metaflumizone poisoning in humans is still unknown.

CASE DETAILS: A 57-year-old man presented with a decreased mentality following ingestion of 100 ml of metaflumizone, 150 ml of glyphosate and alcohol. Although initial methemoglobin (MetHb) level was slightly higher than the normal limit, it gradually rose to reach a maximum level of 27.8%, on the 19 h after ingestion. After hemodialysis, MetHb level was reduced to 15.8%, which decreased further to the level of 6%, following methylene blue administration. DISCUSSION: Metaflumizone shares a similar chemical structure to indoxacarb, which is known to be a cause of methemoglobinemia. Physicians should be alert for the development of methemoglobinemia in symptomatic patients when facing potential pesticide poisoning such as metaflumizone poisoning.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2012", "Paetow, L. J., Daniel McLaughlin, J., Cue, R. I., Pauli, B. D., Marcogliese, D. J.", "Effects of herbicides and the chytrid fungus *Batrachochytrium dendrobatidis* on the health of post-metamorphic northern leopard frogs (*Lithobates pipiens*)", "Ecotoxicology and environmental safety", "80:372-80", "5243ec3e-3088-41fa-bdcd-99935ffc3a47", "", "Effects of exposure to contaminants such as pesticides along with exposure to pathogens have been listed as two major contributors to the global crisis of declining amphibian populations. These two factors have also been linked in explanations of the causes of these population declines. We conducted a combined exposure experiment to test the hypothesis that exposure to two agricultural herbicides would increase the susceptibility of post-metamorphic northern leopard frogs (*Lithobates pipiens*) to the amphibian fungal pathogen *Batrachochytrium dendrobatidis* (Bd). We assessed the independent and interactive effects of these exposures on the health and survival of the frogs. Wild-caught frogs underwent a 21-day exposure to a nominal concentration of either 2.1 mug/L atrazine (Aatrex((R)) Liquid 480) or 100 mug a.e./L glyphosate (Roundup((R)) Original), followed by Bd, and then were observed until 94 days post-initial exposure to the

herbicides. Actual levels of atrazine were between 4.28 +/- 0.04 mug/L and 1.70 +/- 0.26 mug/L while glyphosate degraded from 100 mug a.e./L to approximately 7 mug a.e./L within 6 days of initial exposure to the herbicides. Compared to controls, the glyphosate formulation reduced the snout-vent length of frogs during the pesticide exposure (at Day 21), and the atrazine formulation reduced gain in mass up to Day 94. No treatment affected survival, splenosomatic or hepatosomatic indices, the densities and sizes of hepatic and splenic melanomacrophage aggregates, the density and size of hepatic granulomas, proportions of circulating leucocytes, the ratio of neutrophils to lymphocytes, or the ratio of leucocytes to erythrocytes. Histological assessment of samples collected at Day 94 revealed no evidence of Bd infection in any Bd-exposed frogs, while real-time PCR detected only one case of light infection in a single atrazine- and Bd-exposed frog. Frogs exposed to Bd shed their skin significantly more frequently than Bd-unexposed frogs, which may have helped them resist or clear infection, and could explain why no interaction between the herbicides and Bd was detected. The results suggest that these frogs were resistant to Bd infection and that pre-exposure to the herbicides did not alter this resistance. The effects seen on the growth following herbicide exposure is a concern, as reduced growth can lower the reproductive success and survival of the amphibians."

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"Unknown","Unknown","Unknown","Unknown",","","","2010","Paganelli, A., Gnazzo, V., Acosta, H., Lopez, S. L., Carrasco, A. E.", "Glyphosate-based herbicides produce teratogenic effects on vertebrates by impairing retinoic acid signaling", "Chemical research in toxicology", "23(10):1586-95", "52cbccff-cc73-467b-a26b-0b4b334212cf", ",","The broad spectrum herbicide glyphosate is widely used in agriculture worldwide. There has been ongoing controversy regarding the possible adverse effects of glyphosate on the environment and on human health. Reports of neural defects and craniofacial malformations from regions where glyphosate-based herbicides (GBH) are used led us to undertake an embryological approach to explore the effects of low doses of glyphosate in development. *Xenopus laevis* embryos were incubated with 1/5000 dilutions of a commercial GBH. The treated embryos were highly abnormal with marked alterations in cephalic and neural crest development and shortening of the anterior-posterior (A-P) axis. Alterations on neural crest markers were later correlated with deformities in the cranial cartilages at tadpole stages. Embryos injected with pure glyphosate showed very similar phenotypes. Moreover, GBH produced similar effects in chicken embryos, showing a gradual loss of rhombomere domains, reduction of the optic vesicles, and microcephaly. This suggests that glyphosate itself was responsible for the phenotypes observed, rather than a surfactant or other component of the commercial formulation. A reporter gene assay revealed that GBH treatment increased endogenous retinoic acid (RA) activity in *Xenopus* embryos and cotreatment with a RA antagonist rescued the teratogenic effects of the GBH. Therefore, we conclude that the phenotypes produced by GBH are mainly a consequence of the increase of endogenous retinoid activity. This is consistent with the decrease of Sonic hedgehog (Shh) signaling from the embryonic dorsal midline, with the inhibition of *otx2* expression and with the disruption of cephalic neural crest development. The direct effect of glyphosate on early mechanisms of morphogenesis in vertebrate embryos opens concerns about the clinical findings from human offspring in populations exposed to GBH in agricultural fields."

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Spinelli, J. J., Blair, A., Pahwa, P., Dosman, J. A., McLaughlin, J. R., Demers, P. A., Zahm, S. H., Cantor, K. P., Weisenburger, D. D., Harris, S. A.", "The North American Pooled Project (NAPP): Pooled analyses of case-control studies of pesticides and agricultural exposures, lymphohematopoietic cancers and sarcoma", "", "71:A116", "dcf90218-1e2a-4da1-8cc5-cb9910941c0c", "", "Objectives Previous studies have noted associations between specific pesticides and multiple cancer types. However, assessments for many pesticides have been limited by small numbers of exposed cases. To address this, we established the North American Pooled Project (NAPP), a collaborative effort to evaluate the relationship of pesticide and agricultural exposures to risks of lymphohematopoietic cancers and sarcoma. Method We harmonised previously collected data from three population-based case-control studies conducted in four American states with a similar Canada-wide study conducted in six provinces. Descriptive analyses of pesticide exposures, personal protective equipment (PPE) use, and demographic data were completed. The prevalence of self-reported pesticide use among cases and controls was determined for specific agents and chemical classes. Results The NAPP includes 5131 controls and 3274 cases (non-Hodgkin lymphoma [NHL] N=1690; Hodgkin lymphoma [HL] N=507; multiple myeloma [MM] N=587; soft tissue sarcoma N=490). Preliminary descriptive analyses indicate that approximately two-thirds of controls and NHL and MM cases ever lived or worked on a farm or ranch. Nearly half of controls and half of NHL, HL, and MM cases reported using any pesticide. Over 120 different insecticides, herbicides, and fungicides were reported. More than 17% of participants reported using the phenoxy herbicide 2,4-D and over 5% reported DDT, malathion, atrazine, or glyphosate. Around 6% of NHL cases and controls reported ever using PPE. Conclusions The large number of cases and controls and high frequency of pesticide use in the NAPP will allow us to evaluate less commonly used pesticides, cancer sub-types, and smaller relative risks than previously possible.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2002", "Panagopoulou, E., Kouloukoussa, M., Voloudaki-Baltatzi, I., Kittas, C., Marinou, E.", "The effect of 12-O-tetradecanoylphorbol-13-acetate on Sertoli cell morphology and cytoskeletal organization: an in vitro study by means of cryo-SEM and fluorescent techniques", "Biology of the cell / under the auspices of the European Cell Biology Organization", "94(2):117-25", "979b2489-ald1-4a5c-9cab-a6a9bfae0cd6", "", "By means of cryo-scanning electron microscopy (cryo-SEM) and fluorescent techniques, evidence is provided on how 12-O-tetradecanoylphorbol-13-acetate (TPA) affects Sertoli cell morphology and F-actin and vinculin organization in vitro. In order to visualize the morphological changes, the cells were observed with cryo-SEM. F-actin was localized using rhodamine (TRI)-phalloidin and vinculin using a primary monoclonal antibody and a second TRI-conjugated antibody. The results indicate that after the addition of 10(-7) M TPA, Sertoli cells begin to round up and their cytoplasm is retracted towards a central region. Actin bundle organization is disrupted and vinculin assumes a punctuate distribution throughout the cell. Thus, the reorganization of actin and vinculin and subsequent changes in cell morphology seem to be brought about by TPA affecting not only actin but also the protein vinculin which interacts with actin. A discussion is made concerning the effect of TPA on cytoskeletal reorganization, which is closely related to cell transformation.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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simple life cycle, exhibiting only the trophozoitic form. However, under unfavorable growth conditions, the trophozoites, which are polar and flagellated, can round up and internalize their flagella forming pseudocysts. In this form no cyst wall surrounds the cell and it also displays a distinct mitosis when compared with the trophozoite form. In pseudocyst mitosis, the cell proceeds with duplication of cytoskeletal and mastigont structures; nuclear division occurs but without the corresponding cytoplasm division. Thus, giant multinucleated cells which present many mastigont structures are formed (approximately 62% of the population). These polymastigont/multinucleated cells are maintained when the cells are under stress conditions. When environmental conditions become favorable, the flagella are externalized and new flagellated trophozoites one by one, gradually bud from the multinucleated cell. Thus, in order to better understand the pseudocyst mitosis, the polymastigont formation and the generation of new cells by this budding process, video microscopy and other complementary techniques, such as immunofluorescence and transmission electron microscopy were

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Antituberculosis treatment had been completed. CONCLUSION: In the differential diagnosis of an ovarian tumor and ascites TB should always be considered. It should also be suspected in recent Mycobacterium tuberculosis infection in younger women with amenorrhea, either HIV-seropositive or not.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"safety" of this herbicide. Investigations concerning both its accumulation and toxic effect in animals and plants are now under way in many laboratories.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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of common herbicides and insecticides on expression of urokinase and its receptor, uPAR. The herbicide Roundup and insecticides Lorsban and Warrior induced uPA while Lorsban and Warrior also induced uPAR. Furthermore, a combination of Roundup + Lorsban or Roundup + Warrior produced greater increases in uPA and uPAR than when agents were used alone. Both active and "inactive" chemicals within these pesticides are important for the effects observed as the neat chemicals alone failed to induce uPA and were less potent inducers of uPAR. Thus, specific pesticide formulations, especially when combined, can increase uPA and uPAR expression in vitro in transformed prostate epithelial cells.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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little effect on tumour growth. In contrast, the same dose of 2-MeOEMATE resulted in the almost complete regression of 2/3 tumours over an 11-day period. We conclude that 2-MeOEMATE should have considerable therapeutic potential for the treatment of breast tumours.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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herbicides toxicity, a different approach", "", "278:186", "f2dd5060-b6eb-4fc2-839c-e46897531801", "", "(Sociedad Española de Bioquímica y Biología Molecular) Glyphosate is, probably, the most commercialized broad-spectrum herbicide worldwide. People may be exposed to its residues by agricultural practices or along the food chain. With respect to toxicity, harmful effects are described in several models, not only human. Among these effects are: cell cycle modifications, apoptosis and necrosis induction or alternations in gene transcription. We studied glyphosate toxicity in the human prostate cancer cell lines PC3 (androgen independent) and LNCap (androgen dependant). Results in cell proliferation by MTT salts metabolization, show a decrease in cell number up to a 60%, after 3 days of treatment with 50-100  $\mu$ M glyphosate supplemented medium. Apoptosis induction analysis performed detecting Annexin-V by flow cytometry and valuating Procaspase-3 activation, shows an increase of apoptotic cells referred to control in both lines. Lactate Dehydrogenase (LDH) liberation assays indicate that there are significant levels of necrosis in LNCap line, but not in PC3. A primary study with propidium iodide by flow cytometry, apparently shows cell cycle alterations as well. All these effects, previously mentioned in other models, seem not to be enough to explain the dramatic decrease in cell viability we observed. That's why we studied an indicator of another cell death pathway: autophagy. Results on LC3 protein expression are highly significant, reaching a 200% signal referred to the control, both for 2 and 3 days of treatment, even before changes in apoptosis induction or LDH liberation are seen. The same occurs with acridine orange staining, which shows not only an increase of acid vesicles but also a redistribution of them. Commonly, all the effects are more intense in the androgen dependant cell line, what lead us to suspect that glyphosate has a differential effect between both models, resulting highly cytotoxic for LNCap and mainly Cytostatic in PC3.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Resnik, D. B.", "Retracting Inconclusive Research: Lessons from the Seralini GM Maize Feeding Study", "Journal of agricultural & environmental ethics", "28(4):621-633", "43800a1f-7e24-46a7-b003-9daff91d3fae", "", "In September 2012, Gilles-Eric Seralini and seven coauthors published an article in Food and Chemical Toxicology claiming that rats fed Roundup(c)-resistant genetically modified maize alone, genetically modified maize with Roundup(c), or Roundup(c) for 2 years had a higher percentage of tumors and kidney and liver damage than normal controls. Shortly after this study was published, numerous scientists and several scientific organizations criticized the research as methodologically and ethically flawed. In January 2014, the journal retracted the article without the authors' consent on the grounds that the research was inconclusive. In June 2014, Environmental Sciences Europe published a slightly modified version of the retracted paper. The publication, retraction and subsequent republication of the Seralini study raise important scientific and ethical issues for journal editors. Decisions to retract an article should be made on the basis of well-established policies. Articles should be retracted only for serious errors that undermine the reliability of the data or results, or for serious ethical lapses, such as research misconduct or mistreatment of animal or human subjects. Inconclusiveness, by itself, is not a sufficient reason for retracting an article, though a flawed study design might be. Retracted articles that are submitted for republication should undergo scientific review to ensure that they meet appropriate standards. Republished articles should be linked to the original, retracted publication. Journals that are reviewing studies with significant scientific and social implications should take special care to ensure that peer review is rigorous

and fair.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2005", "Richard, S., Moslemi, S., Sipahutar, H., Benachour, N., Seralini, G. E.", "Differential effects of glyphosate and roundup on human placental cells and aromatase", "Environmental health perspectives", "113(6):716-20", "6fc4d53a-b403-4cce-9279-8bd01d68b4a4", "", "Roundup is a glyphosate-based herbicide used worldwide, including on most genetically modified plants that have been designed to tolerate it. Its residues may thus enter the food chain, and glyphosate is found as a contaminant in rivers. Some agricultural workers using glyphosate have pregnancy problems, but its mechanism of action in mammals is questioned. Here we show that glyphosate is toxic to human placental JEG3 cells within 18 hr with concentrations lower than those found with agricultural use, and this effect increases with concentration and time or in the presence of Roundup adjuvants. Surprisingly, Roundup is always more toxic than its active ingredient. We tested the effects of glyphosate and Roundup at lower nontoxic concentrations on aromatase, the enzyme responsible for estrogen synthesis. The glyphosate-based herbicide disrupts aromatase activity and mRNA levels and interacts with the active site of the purified enzyme, but the effects of glyphosate are facilitated by the Roundup formulation in microsomes or in cell culture. We conclude that endocrine and toxic effects of Roundup, not just glyphosate, can be observed in mammals. We suggest that the presence of Roundup adjuvants enhances glyphosate bioavailability and/or bioaccumulation.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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between parental pesticide use and adverse birth outcomes including physical birth defects, low birth weight, and fetal death, although the data are less robust than for cancer and neurodevelopmental effects. Children's exposures to pesticides should be limited as much as possible. Copyright © 2012 by the American Academy of Pediatrics.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "1996", "Ronnov-Jessen, L., Petersen, O. W.", "ADP-ribosylation of actins in fibroblasts and myofibroblasts by botulinum C2 toxin: influence on microfilament morphology and migratory behavior", "Electrophoresis", "17(11):1776-80", "aae4be64-c378-46c1-96eb-192bdd7fe6c5", "", "Actins comprise six isoforms of which the nonmuscle isoforms beta-/gamma-actins are expressed by all eukaryotic cells. The expression pattern of one of the muscle actin isoforms, alpha-sm actin, previously believed to be restricted to smooth muscle, has been broadened to encompass activated fibroblasts (myofibroblasts) as well. The significance of this molecular conversion has remained largely unknown. We have recently shown that a reduction in filamentous alpha-sm actin by electroinjected specific antibodies or antisense oligodeoxynucleotides leads to increased motility in breast myofibroblasts (Ronnov-Jessen, L., Petersen, O. W. J. Cell Biol. 1996, 134, 67-80). In the present study we have expanded on the functional significance of actin isotypes in fibroblasts from the opposite point of view, namely filamentous nonmuscle actin. Nonmuscle actins in fibroblasts and myofibroblasts were ADP-ribosylated by Clostridium botulinum C2 toxin. The substrate for C2 toxin is globular actin, which upon ribosylation cannot incorporate into microfilaments. The pattern of actin ADP-ribosylation in (myo)fibroblasts in the presence of [32P]NAD was analyzed by isoelectric focusing, fluorography and immunoblotting. The influence of C2 toxin on microfilaments in intact cells was further assessed by immunofluorescence, and motility was measured in a mass migration assay and by computerized video time-lapse microscopy. We show here that C2 toxin specifically ribosylates beta- and gamma-actin in both fibroblasts and myofibroblasts. Whereas fibroblasts rapidly round up and stop migrating when filamentous beta-/gamma-actin is reduced by short-term ADP-ribosylation, myofibroblasts maintain their flattened morphology and a basic low motility.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2011", "Rosenmayr-Templeton, L.", "Industry update: The latest developments in therapeutic delivery", "", "2(9):1109-1114", "c6cf6506-84ef-467b-a5c6-9fa027bdb8d1", "", "In addition to the monthly round-up of news on chemistry and formulation-based delivery technologies, this months article includes events affecting four companies taking atypical approaches to dealing with serious but everyday unmet clinical needs. These include Amorceyte, Inc., a company with an autologous cell-based therapy to limit heart muscle damage following myocardial infarction. The second is Audion Therapeutics, whose goal is to develop medicines that will regenerate sensory hair cells in the inner ear and, in doing so, correct hearing loss. The third is Neurowave Medical Technologies which launched its Nometexâ„¢ transdermal neuromodulation device for the treatment of acute and delayed chemotherapy-induced nausea and vomiting in July. Last but not least Proteus was granted a US patent for its ingestible event marker that can be incorporated into solid dosage forms and

used to monitor medication compliance and other therapeutic relevant metrics. As ever, the information is mainly sourced from press releases and company websites. The article covers the period 16 June 2011 to 15 July 2011. © 2011 Future Science

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2008", "Sakamoto, Y., Tada, Y., Fukumori, N., Tayama, K., Ando, H., Takahashi, H., Kubo, Y., Nagasawa, A., Yano, N., Yuzawa, K., Ogata, A.", "[A 104-week feeding study of genetically modified soybeans in F344 rats]", "Shokuhin eiseigaku zasshi. Journal of the Food Hygienic Society of Japan", "49(4):272-82", "c86f9d96-ef21-473e-8c5c-3ae61b54b393", "", "A chronic feeding study to evaluate the safety of genetically modified glyphosate-tolerant soybeans (GM soybeans) was conducted using F344 DuCrj rats. The rats were fed diet containing GM soybeans or Non-GM soybeans at the concentration of 30% in basal diet. Non-GM soybeans were a closely related strain to the GM soybeans. These two diets were adjusted to an identical nutrient level. In this study, the influence of GM soybeans in rats was compared with that of the Non-GM soybeans, and furthermore, to assess the effect of soybeans themselves, the groups of rats fed GM and Non-GM soybeans were compared with a group fed commercial diet (CE-2). General conditions were observed daily and body weight and food consumption were recorded. At the termination (104 weeks), animals were subjected to hematology, serum biochemistry, and pathological examinations. There were several differences in animal growth, food intake, organ weights and histological findings between the rats fed the GM and/or Non-GM soybeans and the rats fed CE-2. However, body weight and food intake were similar for the rats fed the GM and Non-GM soybeans. Gross necropsy findings, hematological and serum biochemical parameters, and organ weights showed no meaningful difference between rats fed the GM and Non-GM soybeans. In pathological observation, there was neither an increase in incidence nor any specific type of nonneoplastic or neoplastic lesions in the GM soybeans group in each sex. These results indicate that long-term intake of GM soybeans at the level of 30% in diet has no apparent adverse effect in

rats.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Samet, J. M.", "The IARC monographs: Critics and controversy", "", "36(7):707-709", "148be60f-096f-406e-b1ca-6e624f60f384", "", "The monograph program of the International Agency for Research on Cancer (IARC), which relies on the efforts of volunteer Working Groups, uses a transparent approach to evaluate the carcinogenicity of agents for which scoping has determined that there is sufficient evidence to warrant a review. Because of the potentially powerful implications of the conclusions of the monographs and the sometimes challenging nature of the evidence reviewed, the monographs and the IARC process have been criticized from time to time. This commentary describes the IARC monograph process and addresses recent criticisms of the program, drawing on a recent defense of the program authored by 124 researchers. These authors concluded that the IARC processes are robust and transparent and not flawed and biased as suggested by some critics.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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macrocytic anemia and depression. It is a multifactorial disease associated with numerous nutritional deficiencies as well as reproductive issues and increased risk to thyroid disease, kidney failure and cancer. Here, we propose that glyphosate, the active ingredient in the herbicide, Roundup((R)), is the most important causal factor in this epidemic. Fish exposed to glyphosate develop digestive problems that are reminiscent of celiac disease. Celiac disease is associated with imbalances in gut bacteria that can be fully explained by the known effects of glyphosate on gut bacteria. Characteristics of celiac disease point to impairment in many cytochrome P450 enzymes, which are involved with detoxifying environmental toxins, activating vitamin D3, catabolizing vitamin A, and maintaining bile acid production and sulfate supplies to the gut. Glyphosate is known to inhibit cytochrome P450 enzymes. Deficiencies in iron, cobalt, molybdenum, copper and other rare metals associated with celiac disease can be attributed to glyphosate's strong ability to chelate these elements. Deficiencies in tryptophan, tyrosine, methionine and selenomethionine associated with celiac disease match glyphosate's known depletion of these amino acids. Celiac disease patients have an increased risk to non-Hodgkin's lymphoma, which has also been implicated in glyphosate exposure. Reproductive issues associated with celiac disease, such as infertility, miscarriages, and birth defects, can also be explained by glyphosate. Glyphosate residues in wheat and other crops are likely increasing recently due to the growing practice of crop desiccation just prior to the harvest. We argue that the practice of "ripening" sugar cane with glyphosate may explain the recent surge in kidney failure among agricultural workers in Central America. We conclude with a plea to governments to reconsider policies regarding the safety of glyphosate residues in foods.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2005", "Sanden, M., Berntssen, M. H., Krogdahl, A., Hemre, G. I., Bakke-McKellep, A. M.", "An examination of the intestinal tract of Atlantic salmon, *Salmo salar* L., parr fed different varieties of soy and maize", "Journal of fish diseases", "28(6):317-30", "a713a0c2-63f2-4826-8d08-c2a47ece011c", "", "This study was conducted to investigate the long-term effects of feeding plant products from both traditional breeding and from biotechnology on intestinal somatic indices, histology and cell proliferation in first-feeding Atlantic salmon, *Salmo salar* L. (initial weight 0.21 +/- 0.02 g). A standard fishmeal diet (standard fishmeal) was formulated to contain fishmeal as the sole protein source and suprex maize as the main starch source. Six experimental diets were then developed: two in which some of the fishmeal was replaced with commercially available, genetically modified Roundup Ready full-fat soybean meal (GM-soy) or commercially available, non-GM full-fat soybean meal (nGM-soy) at a level of 12.5% of the total diet, and four diets in which the suprex maize was replaced with two lines of GM-maize (Dekalb 1; D1 and Pioneer 1; P1), both products of event MON810, and their half-sibling non-GM counterparts (Dekalb 2; D2 and Pioneer 2; P2), at a level of 12.1% of total diet. Each diet was fed to fish in triplicate tanks and the experiment lasted for 8 months, during which the fish reached a final weight of 101-116 g. There was no significant effect of diet on the intestinal indices, nor were histological changes observed in the pyloric caeca or mid intestine. In the distal intestine, one of nine sampled fish fed nGM-soy showed moderate changes, two of nine sampled fish fed GM-soy showed changes, one with moderate and one with severe changes, and two of nine fish fed nGM-maize D2 had moderate changes. Using a monoclonal antibody against proliferating cell nuclear antigen (PCNA), cell proliferative responses to the experimental diets were assessed.

In fish fed both soy diets, a significantly higher ( $P < 0.05$ ) cell proliferation response was observed in the distal intestine concomitant with an increased localization of PCNA positive cells along the whole distal intestinal folds. The PCNA response among the nGM-soy group was significantly higher compared with all the other diet groups. In contrast, for fish exposed to dietary maize (type D) compared with fish fed the standard fishmeal, the soy-diets (GM-soy and nGM-soy) and maize (type P), a significantly lower ( $P < 0.05$ ) cell proliferation response was observed in the distal intestine. Results indicated that the GM plant products investigated in this study, at about 12% inclusion level, were as safe as commercially available non-GM products, at least in terms of their effect on indices and histological parameters of the Atlantic salmon intestinal tract.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

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Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis", "International journal of environmental research and public health", "11(4):4449-527", "e79c966e-d676-491a-b549-942561e9d90b", "", "This paper describes results from a systematic review and a series of meta-analyses of nearly three decades worth of epidemiologic research on the relationship between non-Hodgkin lymphoma (NHL) and occupational exposure to agricultural pesticide active ingredients and chemical groups. Estimates of associations of NHL with 21 pesticide chemical groups and 80 active ingredients were extracted from 44 papers, all of which reported results from analyses of studies conducted in high-income countries. Random effects meta-analyses showed that phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and the active ingredient lindane, an organochlorine insecticide, were positively associated with NHL. In a handful of papers, associations between pesticides and NHL subtypes were reported; B cell lymphoma was positively associated with phenoxy herbicides and the organophosphorus herbicide glyphosate. Diffuse large B-cell lymphoma was positively associated with phenoxy herbicide exposure. Despite compelling evidence that NHL is associated with certain chemicals, this review indicates the need for investigations of a larger variety of pesticides in more geographic areas, especially in low- and middle-income countries, which, despite producing a large portion of the world's agriculture, were missing in the literature that were

reviewed.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2009", "Schneider, M. I., Sanchez, N., Pineda, S., Chi, H., Ronco, A.", "Impact of glyphosate on the development, fertility and demography of *Chrysoperla externa* (Neuroptera: Chrysopidae): ecological approach", "Chemosphere", "76(10):1451-5", "90edc9d5-7c9a-425d-b036-dad1cdf7aacb", "", "Few ecotoxicological studies have used life table analysis to evaluate the toxicity of pesticides on beneficial organisms. This study is the first report of the effect of the herbicide glyphosate on a predator insect, *Chrysoperla externa*, using a demographic approach. This predator is associated to soybean pests and has a potential role as a biological control agent in the Neotropical Region. The objective of this work was to evaluate the side-effects of glyphosate on the development, fertility and demography of *C. externa*, treated orally by ingestion of glyphosate-dipped eggs of *Sitotroga cerealella* in laboratory conditions. The data were analyzed using the age-stage, two-sex life table. Development from third larval instar to pupae and adult longevity were shorter in glyphosate-treatment than in the control. Adult pre-reproductive period was longer in glyphosate-treatment than in the control. Fecundity and fertility were deeply reduced, as well, being fertility greater affected. A high important reduction was registered in all population parameters. Most eggs from glyphosate-treated cohort looked abnormal, smaller than control, dehydrated and became black 2d after oviposition. In addition, adults developed tumours in the abdomen region at 20d after emergence, being the effect more drastic in females than males. It is beyond the scope of our study to speculate on the effects of this herbicide on *C. externa* field populations. However, it seems likely that populations under continuous use of glyphosate would be exposed at greater detrimental effects in the long term.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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70", "db7fbalf-ae3a-4471-bddd-9d5ac7616d0b", "", "IL-6 has been found to be a potent inhibitor of melanoma A375-C6 cell adhesion, in addition to its known action in arresting cells at G1/G0 phase of the cell cycle IL-6 treated melanoma cells were found to round up and to lose the ability to adhere to fibronectin, laminin, collagen, and tenascin over 72 to 96 hours of IL-6 treatment, a time course similar to that seen for cell cycle inhibition. Cell cycle inhibition and loss of adhesion were found, however, to be independent effects of IL-6. Analysis of cell surface integrins indicated significant changes in the expression of several integrins including downregulation of  $\alpha 3$  and  $\alpha v \beta 5$  and upregulation of  $\alpha 3$ . However, the changes in integrin expression did not correlate with loss of adhesion to relevant ligands. Three A375 melanoma clones varying in metastatic potential also demonstrated inhibition of both cell proliferation and matrix adhesion by IL-6.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2011", "Sen, S., Ng, W. P., Kumar, S.", "Contractility dominates adhesive ligand density in regulating cellular de-adhesion and retraction kinetics", "Annals of biomedical engineering", "39(4):1163-73", "9e61f0a2-d155-4d2f-a3e5-14ebe8f4702a", "", "Cells that are enzymatically detached from a solid substrate rapidly round up as the tensile prestress in the cytoskeleton is suddenly unopposed by cell-ECM adhesions. We recently showed that this retraction follows sigmoidal kinetics with time constants that correlate closely with cortical stiffness values. This raises the promising prospect that these de-adhesion measurements may be used for high-throughput screening of cell mechanical properties; however, an important limitation to doing so is the possibility that the retraction kinetics may also be influenced and potentially rate-limited by the time needed to sever matrix adhesions. In this study, we address this open question by separating contributions of contractility and adhesion to cellular de-adhesion and retraction kinetics. We first develop serum-free conditions under which U373 MG glioma cells can be cultured on substrates of fixed fibronectin density without direct matrix contributions from the medium. We show that while spreading area increases with ECM protein density, cortical stiffness and the time constants of retraction do not. Conversely, addition of lysophosphatidic acid (LPA) to stimulate cell contractility strongly speeds retraction, independent of the initial matrix protein density and LPA's contributions to spreading area. All of these trends hold in serum-rich medium commonly used in tissue culture, with the time constants of retraction much more closely tracking cortical stiffness than adhesive ligand density or cell spreading. These results support the use of cellular de-adhesion measurements to track cellular mechanical properties.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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organ; the sex hormonal balance was modified by GMO and Roundup treatments. In treated males, liver congestions and necrosis were 2.5-5.5 times higher. This pathology was confirmed by optic and transmission electron microscopy. Marked and severe kidney nephropathies were also generally 1.3-2.3 greater. Males presented 4 times more large palpable tumors than controls which occurred up to 600 days earlier. Biochemistry data confirmed very significant kidney chronic deficiencies; for all treatments and both sexes, 76% of the altered parameters were kidney related. These results can be explained by the non linear endocrine-disrupting effects of Roundup, but also by the overexpression of the transgene in the GMO and its metabolic consequences.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2013", "S  ralini, G. E., Mesnage, R., Defarge, N., Gress, S., Hennequin, D., Clair, E., Malatesta, M., de Vend  mois, J. S.", "Answers to critics: Why there is a long term toxicity due to a Roundup-tolerant genetically modified maize and to a Roundup herbicide", "", "53:461-468", "a60d4deb-cc19-4aed-ala7-388aaf90a840", "", "Our recent work (S  ralini et al., 2012) remains to date the most detailed study involving the life-long consumption of an agricultural genetically modified organism (GMO). This is true especially for NK603 maize for which only a 90-day test for commercial release was previously conducted using the same rat strain (Hammond et al., 2004). It is also the first long term detailed research on mammals exposed to a highly diluted pesticide in its total formulation with adjuvants. This may explain why 75% of our first criticisms arising within a week, among publishing authors, come from plant biologists, some developing patents on GMOs, even if it was a toxicological paper on mammals, and from Monsanto Company who owns both the NK603 GM maize and Roundup herbicide (R). Our study has limits like any one, and here we carefully answer to all criticisms from agencies, consultants and scientists, that were sent to the Editor or to ourselves. At this level, a full debate is biased if the toxicity tests on mammals of NK603 and R obtained by Monsanto Company remain confidential and thus unavailable in an electronic format for the whole scientific community to conduct independent scrutiny of the raw data. In our article, the conclusions of long-term NK603 and Roundup toxicities came from the statistically highly discriminant findings at the biochemical level in treated groups in comparison to controls, because these findings do correspond in an blinded analysis to the pathologies observed in organs, that were in turn linked to the deaths by anatomopathologists. GM NK603 and R cannot be regarded as safe to date.    2012 Elsevier Ltd.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "1996", "Shelden, E., Wadsworth, P.", "Stimulation of microtubule dynamic turnover in living cells treated with okadaic acid", "Cell motility and the cytoskeleton", "35(1):24-34", "flbdf4eb-ae94-40e6-9ffe-cd907e419f65", "", "We have examined the effects of okadaic acid, an inhibitor of protein phosphatases type 1 and 2A, on the dynamic instability behavior of individual microtubules in living cells. Addition of 1 microM okadaic acid to PtK1 epithelial cells induced ruffling of lamellar regions; after 50 min in okadaic acid, many cells were observed to round up. Confocal microscopy of okadaic acid-treated cells stained with an antibody to tubulin showed that microtubules were more densely packed near the periphery of the rounded cells, and in many cells, a reduction in the density of microtubules near the microtubule-organizing center was observed. The dynamic behavior of individual microtubules in cells previously injected with rhodamine-labeled tubulin was quantified by tracking individual microtubules from image sequences. Microtubule

dynamic turnover was markedly stimulated in cells treated with 1 microM okadaic acid for 50-60 min: The average rates of both microtubule growing and shortening increased, and the average duration of pause, or attenuation, a phase in which neither growth nor shortening could be detected, was significantly decreased. Further, okadaic acid induced an approximately twofold increase in the frequency of catastrophe transitions and a threefold decrease in the frequency of rescue transitions. Dynamicity, a measure of the net gain and loss of polymer at microtubule plus ends, increased nearly threefold in okadaic acid-treated cells. These results demonstrate that microtubule turnover is stimulated in okadaic acid-treated cells and suggest that phosphorylation of molecules which interact with microtubules may result in increased microtubule dynamic turnover in vivo.

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"Unknown","Unknown","Unknown","Unknown",,"","2016","Singh, B., Singh, K.,"Microbial degradation of herbicides",,"42(2):245-261","041bdb4e-bbb1-486b-a94c-1583506e1670",,"Herbicides remain the most effective, efficient and economical way to control weeds; and its market continues to grow even with the plethora of generic products. With the development of herbicide-tolerant crops, use of herbicides is increasing around the world that has resulted in severe contamination of the environment. The strategies are now being developed to clean these substances in an economical and eco-friendly manner. In this review, an attempt has been made to pool all the available literature on the biodegradation of key herbicides, clodinafop propargyl, 2,4-dichlorophenoxyacetic acid, atrazine, metolachlor, diuron, glyphosate, imazapyr, pendimethalin and paraquat under the following objectives: (1) to highlight the general characteristic and mode of action, (2) to enlist toxicity in animals, (3) to pool microorganisms capable of degrading herbicides, (4) to discuss the assessment of herbicides degradation by efficient microbes, (5) to highlight biodegradation pathways, (6) to discuss the molecular basis of degradation, (7) to enlist the products of herbicides under degradation process, (8) to highlight the factors effecting biodegradation of herbicides and (9) to discuss the future aspects of herbicides degradation. This review may be useful in developing safer and economic microbiological methods for cleanup of soil and water contaminated with such compounds.

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"Unknown","Unknown","Unknown","Unknown",,"","2010","Slager, R. E., Simpson, S. L., Levan, T. D., Poole, J. A., Sandler, D. P., Hoppin, J. A.,"Rhinitis associated with pesticide use among private pesticide applicators in the agricultural health study",,"Journal of toxicology and environmental health. Part A",,"73(20):1382-93",,"c2a8caab-e801-488c-9cef-f4f113aebaf5",,"Farmers commonly experience rhinitis but the risk factors are not well characterized. The aim of this study was to analyze cross-sectional data on rhinitis in the past year and pesticide use from 21,958 Iowa and North Carolina farmers in the Agricultural Health Study, enrolled 1993-1997, to evaluate pesticide predictors of rhinitis. Polytomous and logistic regression models were used to assess association between pesticide use and rhinitis while controlling for demographics and farm-related exposures. Sixty-seven percent of farmers reported current rhinitis and 39% reported 3 or more rhinitis episodes. The herbicides glyphosate [odds ratio (OR) = 1.09, 95% confidence interval (95% CI) = 1.05-1.13] and petroleum oil (OR = 1.12, 95% CI = 1.05-1.19) were associated with current rhinitis and increased rhinitis episodes. Of the insecticides, four organophosphates (chlorpyrifos, diazinon, dichlorvos, and malathion), carbaryl, and use of permethrin on animals were predictors of current rhinitis. Diazinon was significant in the overall polytomous

model and was associated with an elevated OR of 13+ rhinitis episodes (13+ episodes OR = 1.23, 95% CI = 1.09-1.38). The fungicide captan was also a significant predictor of rhinitis. Use of petroleum oil, use of malathion, use of permethrin, and use of the herbicide metolachlor were significant in exposure-response polytomous models. Specific pesticides may contribute to rhinitis in farmers; agricultural activities did not explain these findings.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2004", "Smith, T. K., Lund, E. K., Parker, M. L., Clarke, R. G., Johnson, I. T.", "Allyl-isothiocyanate causes mitotic block, loss of cell adhesion and disrupted cytoskeletal structure in HT29 cells", "Carcinogenesis", "25(8):1409-15", "e9689717-8bf2-442c-b462-bf93d51e5c3b", "", "Epidemiological evidence indicates that Brassica vegetables protect against colorectal cancer. Brassicas contain glucosinolates, the breakdown products of which exert antiproliferative effects against cancer cells. We have examined the effects of allyl-isothiocyanate (AITC), a major breakdown product of the glucosinolate sinigrin, on proliferation and death of colorectal cancer cells. HT-29 colorectal cells were exposed to AITC for 24 h and the number of adherent and detached cells determined. Both populations were analysed for cell-cycle characteristics and examined by light and electron microscopy for features of apoptosis and mitosis. Evidence of apoptosis was also determined by flow cytometric analysis of Annexin V staining in the detached population of cells. AITC-treated cells were also stained for alpha-tubulin. Treatment caused cells to round up after 7 h of exposure and subsequently detach. At 24 h these cells were blocked in mitosis. Detached AITC-treated cells showed no signs of apoptosis as assessed by morphological features or by Annexin V staining but they did show evidence of disrupted tubulin. AITC inhibits proliferation of cancer cells by causing mitotic block associated with disruption of alpha-tubulin in a manner analogous to a number of chemotherapeutic agents.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2001", "Sodachanh, D., Benghuzzi, H., Tucci, M., Cason, Z.", "The effect of thyroid stimulating hormone on the proliferation and viability of HEP-2 laryngeal cells in culture", "Biomedical sciences instrumentation", "37:149-54", "a873a551-b2f4-4f41-8f46-581fe36e17a9", "", "The objective of this experiment was to study the effect of TSH on Hep-2 cells. A total of sixteen tubes (5 x 10<sup>4</sup>) cells per tube) were divided into four equal groups (media alone (control), serum containing 0 TSH, 10.3 microliters/ml TSH, and 49 microliters/ml TSH). The supernatants and cells were collected at 24, 48, and 72 hours after incubation. The result show that TSH caused an increase in cell number after 24 hours in comparison to control media alone. Analysis of supernatants for cellular damage showed an increased pattern in MDA levels in serum exposed cells at 24, 48, and 72 hours. In contrast, MDA levels in TSH treated cells were similar at 24, 48, and 72 hours. The levels obtained at 48 and 72 hours were statistically (P < 0.05) lower than those obtained for control and serum treated or 0 TSH group. This observation suggests that TSH could provide a protective measure against membrane lipid peroxidation. Morphological evaluation of the cells at 24, 48, and 72 hours, suggests that TSH exposure did induce noticeable cellular injury and most adaptive responses observed were shape changes (round up), cellular detachment, and hyperchromatic nuclei (decrease in cell number).", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2012", "Sorahan, T.", "Multiple myeloma and glyphosate use: A re-analysis of US Agricultural Health Study data", "", "211:S127", "2889391d-7acb-4b3d-8865-c3cdeaaadc18", "", "A follow-up study of

57,311 US pesticide applicators enrolled in the US Agricultural Health Study (AHS) identified 32 cases of multiple myeloma (De Roos et al., 2005). Analyses in relation to ever-use of glyphosate produced disparate findings. Risks were unexceptional (RR = 1.1) when all study subjects were included, with adjustment for age only. However a non-significant elevated risk (RR = 2.6) was reported after adjustment for many variables and when subjects with missing data for any of these variables were excluded (22 cases remaining). Such differences are unusual and it seemed important to understand how they came about and which result should be given more importance. A Poisson regression analysis similar to that employed by the original researchers was used, except that subjects with missing data were not excluded. Instead 'not known' categories were used for each variable (e.g. lifetime smoking now had four possible values: never, no more than 12 pack-years, more than 12 pack-years, not known). With analysis of the full dataset, adjustment for age only produced a relative risk of 1.1 (95% CI 0.5-2.4) for ever use of glyphosate. Additional adjustment for education, smoking, alcohol use, family history of cancer and use of ten other pesticides had little effect (RR = 1.2, 95% CI 0.5 to 2.9). The exclusion of subjects with missing data for aetiologically irrelevant variables is not to be recommended, and currently, there is no good evidence in the AHS for a link between multiple myeloma and ever use of

glyphosate.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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data", "International journal of environmental research and public health", "12(2):1548-

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pesticide applicators enrolled in the US Agricultural Health Study (AHS) produced disparate findings in relation to multiple myeloma risks in the period 1993-2001 and ever-use of glyphosate (32 cases of multiple myeloma in the full dataset of 54,315 applicators without adjustment for other variables: rate ratio (RR) 1.1, 95% confidence interval (CI) 0.5 to 2.4; 22 cases of multiple myeloma in restricted dataset of 40,719 applicators with adjustment for other variables: RR 2.6, 95% CI 0.7 to 9.4). It seemed important to determine which result should be preferred. RRs for exposed and non-exposed subjects were calculated using Poisson regression; subjects with missing data were not excluded from the main analyses. Using the full dataset adjusted for age and gender the analysis produced a RR of 1.12 (95% CI 0.50 to 2.49) for ever-use of glyphosate. Additional adjustment for lifestyle factors and use of ten other pesticides had little effect (RR 1.24, 95% CI 0.52 to 2.94). There were no statistically significant trends for multiple myeloma risks in relation to reported cumulative days (or intensity weighted days) of glyphosate use. The doubling of risk reported previously arose from the use of an unrepresentative restricted dataset and analyses of the full dataset provides no convincing evidence in the AHS for a link between multiple myeloma risk and glyphosate use.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2013", "Sugeng, A. J., Beamer, P. I., Lutz, E. A., Rosales, C. B.", "Hazard-ranking of agricultural pesticides for chronic health effects in Yuma County, Arizona", "", "463-464:35-41", "b06b8a8e-43b7-48f6-ba8b-

220ea5809b23", "", "With thousands of pesticides registered by the United States Environmental Protection Agency, it not feasible to sample for all pesticides applied in agricultural communities. Hazard-ranking pesticides based on use, toxicity, and exposure potential can help prioritize community-specific pesticide hazards. This study applied hazard-ranking schemes for cancer, endocrine disruption, and reproductive/developmental toxicity in Yuma County, Arizona. An existing cancer hazard-ranking scheme was modified, and novel schemes for endocrine disruption and reproductive/developmental toxicity were developed to rank pesticide hazards. The hazard-ranking schemes accounted for pesticide use, toxicity, and exposure potential based on chemical properties of each pesticide. Pesticides were ranked as hazards with respect to each health effect, as well as overall chronic health effects. The highest hazard-ranked pesticides for overall chronic health effects were maneb, metam-sodium, trifluralin, pronamide, and bifenthrin. The relative pesticide rankings were unique for each health effect. The highest hazard-ranked pesticides differed from those most heavily applied, as well as from those previously detected in Yuma homes over a decade ago. The most hazardous pesticides for cancer in Yuma County, Arizona were also different from a previous hazard-ranking applied in California. Hazard-ranking schemes that take into account pesticide use, toxicity, and exposure potential can help prioritize pesticides of greatest health risk in agricultural communities. This study is the first to provide pesticide hazard-rankings for endocrine disruption and reproductive/developmental toxicity based on use, toxicity, and exposure potential. These hazard-ranking schemes can be applied to other agricultural communities for prioritizing community-specific pesticide hazards to target decreasing health risk. © 2013 Elsevier B.V.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "1997", "Sugita, Y., Becerra, S. P., Chader, G. J., Schwartz, J. P.", "Pigment epithelium-derived factor (PEDF) has direct effects on the metabolism and proliferation of microglia and indirect effects on astrocytes", "Journal of neuroscience research", "49(6):710-8", "98b006e9-6d0c-4a25-a115-c669cc7038ff", "", "Pigment epithelium-derived factor (PEDF), a neurotrophic agent first identified in conditioned medium from cultured human retinal pigment epithelial cells, induces neuronal differentiation with neurite outgrowth in Y-79 retinoblastoma cells and has a neurotrophic survival effect on cerebellar granule cells in culture. In the present study, we investigated the effects of human recombinant PEDF (rPEDF) on proliferation and activation of microglia and astrocytes isolated from newborn rat brain. rPEDF treatment caused microglia to round up morphologically, increased their metabolic activity (measured by both MTS conversion and acid phosphatase activity), but blocked proliferation (mitosis). This blocking effect could be demonstrated in cultures stimulated to proliferate by addition of granulocyte-macrophage colony stimulating factor. The effect of rPEDF on microglial metabolic activity showed a dose-response relationship both in serum-containing medium and in chemically defined medium and was blocked with anti-PEDF antibody. rPEDF had no direct effect on the metabolic activity or proliferation of cultured astrocytes but blocked their proliferation in astrocyte-microglia co-cultures. Proliferation of isolated astrocytes was also blocked by conditioned medium from microglia treated with PEDF (PMCM). The effect of PMCM on astrocytes was not blocked by an antibody to transforming growth factor-beta. These results demonstrate that PEDF activates microglial metabolism while blocking proliferation and suggest that a soluble factor(s) released by rPEDF-stimulated microglia blocks the proliferation of astrocytes. Thus, PEDF could play an important

role in regulation of glial function and proliferation in the central nervous system."","","","RefMan","","","","","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2012","Sylvestre Begnis, D., De La Vega, D., Frontini, V., Venera, G.", "Glyphosate-based herbicide-a genotoxic but not epigenic carcinogen. A medium-term RAT model test",","38(9):844","c7113675-765f-4c6d-b738-60f69217794c",","Background: The medium-term rat liver bioassay (Solt & Farber, 1976) has been used by many authors in order to test different types of potentially carcinogen chemical substances. In 1984 Sato introduced detection of placental glutathione-S-transferase enzyme (GSTp) as a preneoplastic altered foci marker in rat liver. It designed a medium term rat liver bioassay based on an initiation and promotion model recommended to test carcinogenicity of substances by the International Conference of Harmonization. Carcinogenicity of herbicide Roundup® has been investigated mostly by its creator Monsanto with unclear results. Objective: To determine carcinogenicity of herbicide Roundup® by the number of initiated cells, the development of preneoplastic hepatic foci and the apoptosis. Design: Prospective, experimental Material and Method: 29 male Wistar rats were randomly divided in three groups. Group 1: Intraperitoneal injection of Diethylnitrosamine (DEN) 150 mg/kg (initiation), an improved two-thirds partial hepatectomy technique (promotion) and Roundup® (2916 mg/kg/day) in drinking water. Group 2: Intraperitoneal injection of DEN and hepatectomy. Group C: Roundup® in water and hepatectomy. At the eighth week animals were sacrificed and liver sections were paraffin embedded. Slices were GSTp immunostained in order to identify the presence of initiated cells and preneoplastic foci. The number and size of initiated cells and altered hepatic foci (AHF) were analyzed and processed with Image Pro Plus software. Apoptotic index was calculated by counting apoptotic bodies in hematoxylin-eosin dyed slices. Results were compared with SPSS 18.0 software (IBM). Results: The number of initiated cells per cm<sup>2</sup> was significantly higher in both groups treated with Roundup® (432 and 423 cells/cm<sup>2</sup> vs. 214, p=0.01). The number of AHF per cm<sup>3</sup> and the relative volume of AHF (mm<sup>3</sup>/cm<sup>3</sup>) showed no difference. Roundup® enhanced the apoptotic index (0.16 and 0.14 in treated groups vs. 0.07 in untreated group, p=0.05) Conclusion: Roundup® significantly enhanced the yield of initiated GSTp positive cells. This demonstrates genotoxic carcinogenicity. There was no development of AHF related to the herbicide administration, so we conclude it is not an epigenetic carcinogen. The enhancement of apoptotic index could be caused by oxidative stress as other authors have demonstrated."","","","RefMan","","","","","","","","","","",""

"Unknown","Unknown","Unknown","Unknown","","","2015","Tango, I., Ezemonye, L.", "Human health risks associated with residual pesticide levels in edible tissues of slaughtered cattle in Benin City, Southern Nigeria",","2:1117-1135","8096f3d0-ac46-4172-8bed-3cbad9a8e42b",","Pesticide residues in meat is of growing concern due to possible adverse effects on humans. Pesticide levels were assessed in five edible cattle parts: muscle, liver, kidney and tongue tissues to determine human health risk associated with consumption of these tissues. Health risk estimates were analysed using estimated daily intake (EDI), hazard quotient (HQ) and hazard index (HI) for two (2) age/weight categories: 1-11years/30. kg for children while 70. kg was used for adult. Risks were categorized for non-carcinogenic and carcinogenic health effects and measured at the average, maximum, 50th and 95th percentiles of the measured exposure concentrations (MEC). Total pesticide residues ranged from 2.38 to 3.86. µg/kg (muscle), 3.58 to 6.3. µg/kg (liver), 1.87 to 4.59. µg/kg (kidney) and 2.54 to 4.35. µg/kg (tongue).

Residual pesticide concentrations in the tissues were in the order: Liver. >. Tongue. >. Muscle. >. Kidney. The concentrations of all the assessed pesticides observed in the tissues were however lower than the recommended maximum residual limits (MRLs). Human health risk estimations for the children showed EDI values for heptachlor epoxide, aldrin and dieldrin exceeding threshold values. Non-cancer risk posed to children on consumption of contaminated cattle parts showed HQ values for heptachlor epoxide, aldrin, dieldrin and HI values for organochlorines exceeding 1, indicating the possibility of non-carcinogenic health risks to consumers especially children from consumption of cattle meat from the selected

abattoirs.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2005", "Tanguy, A., Boutet, I., Moraga, D.", "Molecular characterization of the glutamine synthetase gene in the Pacific oyster *Crassostrea gigas*: expression study in response to xenobiotic exposure and developmental stage", "Biochimica et biophysica acta", "1681(2-3):116-25", "0aa92b0f-4e80-4472-8d57-4977eae674c9", "", "In this study, we characterized the full-length cDNA and genomic sequence of the gene encoding cytosolic glutamine synthetase (CgGSII) in the Pacific oyster, *Crassostrea gigas*. A phylogenetic analysis of GS sequences showed that CgGS clustered with the invertebrate group as expected. We analyzed the expression of mRNA CgGSII using RT-PCR to follow the expression of this gene in gills and digestive gland of oysters exposed, under experimental conditions, to hypoxia and to several contaminants (hydrocarbons and two pesticide treatments, glyphosate and a mixture of atrazine, diuron and isoproturon). We also investigated the expression of CgGSII in different developmental stages of *C. gigas*. Our results show that CgGSII expression was highly regulated in xenobiotic-exposed oysters compared to the control for all the treatments. Likewise, CgGSII expression was highly regulated according to the developmental stage of *C. gigas*. Finally, use of CgGSII as a possible marker to monitor xenobiotic exposure in disturbed ecosystems is

discussed.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Thiam, H. R., Waterman, C. M.", "Spatiotemporal regulation of focal adhesion disassembly at mitosis", "", "26(25)", "9c2b170a-dc38-4e0e-a8f6-61b000afd736", "", "Cell division has two opposite faces: necessary for various physiological processes such as embryogenesis and tissue renewal, it can also lead to death by allowing tumour growth. One hallmark of metazoan cell division is the drastic shape change occurring during mitotic cell rounding. Recent studies have shown that such shape change is required for proper chromosome segregation as well as spindle positioning, orientation and stability. In order for a dividing cell to round up, it must reduce its contact area with the extracellular matrix (ECM), and thus loosen its cell-ECM adhesions. The mechanism allowing dividing cells to spatiotemporally regulate their focal adhesion disassembly at the G2-M transition remains unknown. Using TIRF microscopy, we show here that Vinculin, FAK and Paxillin get dissociated from ECM-bound integrins before nuclear envelope breakdown at mitotic entry leading to focal adhesion disassembly. FAK and calpain have been implicated in focal adhesion disassembly in migrating interphase cells. In order to determine their respective role in focal adhesion disassembly at mitosis, we inhibited FAK and calpain activities using well-characterized inhibitors. We found that while FAK inhibition causes a global defect in mitosis (delay in mitotic entry and cytokinesis), inhibition of calpain led to a drastic inhibition of focal adhesion disassembly at mitotic entry. Our data suggest that focal adhesion disassembly

at mitosis requires calpain proteolysis activity presumably via cleavage of some adaptor proteins such as Talin. The data further suggest that calcium dynamic at mitosis might be a key regulator of focal adhesion

disassembly.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2013", "Thongprakaisang, S., Thiantanawat, A., Rangkadilok, N., Suriyo, T., Satayavivad, J.", "Glyphosate induces human breast cancer cells growth via estrogen receptors", "Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association", "59:129-36", "9cd99a80-bcd7-424e-a3f1-762ef5814b0b", "", "Glyphosate is an active ingredient of the most widely used herbicide and it is believed to be less toxic than other pesticides. However, several recent studies showed its potential adverse health effects to humans as it may be an endocrine disruptor. This study focuses on the effects of pure glyphosate on estrogen receptors (ERs) mediated transcriptional activity and their expressions. Glyphosate exerted proliferative effects only in human hormone-dependent breast cancer, T47D cells, but not in hormone-independent breast cancer, MDA-MB231 cells, at 10(-)(1)(2) to 10(-)(6)M in estrogen withdrawal condition. The proliferative concentrations of glyphosate that induced the activation of estrogen response element (ERE) transcription activity were 5-13 fold of control in T47D-KBluc cells and this activation was inhibited by an estrogen antagonist, ICI 182780, indicating that the estrogenic activity of glyphosate was mediated via ERs. Furthermore, glyphosate also altered both ERalpha and beta expression. These results indicated that low and environmentally relevant concentrations of glyphosate possessed estrogenic activity. Glyphosate-based herbicides are widely used for soybean cultivation, and our results also found that there was an additive estrogenic effect between glyphosate and genistein, a phytoestrogen in soybeans. However, these additive effects of glyphosate contamination in soybeans need further animal study.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "1995", "Torp, S. H., Helseth, E., Unsgaard, G., Dalen, A.", "EGF-effects in vitro and in vivo on a carcinoma cell line rich in EGFR", "Anticancer research", "15(3):667-70", "dda80bd2-4520-4806-8f1d-2caa2cblde7d", "", "T-CAR1 is a human carcinoma cell line established from a brain metastasis. The tumour cells overexpress EGFR and contain an amplified EGFR gene. In vitro in the presence of 5% human serum the tumour cells grow as adherent cells in monolayer. Shortly after exposure to EGF a large number of tumour cells round up and detach, whereas some remain adherent. At the same time a redistribution of actin occurs. Cytochalazin B prevented this reaction, which indicates that actin is involved in the detachment of the tumour cells. The EGF-detached tumour cells however, did not differ from the tumour cells which remained adherent after EGF-exposure with regard to parameters such as growth in soft agar, growth response to EGF, tumour necrosis factor-alpha, interferon-gamma, and carmustin (BCNU), level of EGFR gene expression and EGFR gene amplification, S-phase fraction, and amount of DNA. It was speculated whether the EGF-induced cellular detachment in vitro could be correlated to metastatic potential in vivo or not. In order to address this issue, in vivo studies with subcutaneous T-CAR1 tumours in nude mice were performed. Administration of EGF resulted in growth stimulation in contrast to growth inhibition in vitro, whereas no effect of EGF on the metastatic potential was observed. Thus, the EGF-mediated tumour cell detachment seems to be restricted to in vitro conditions

only.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2010", "Tsai, T. F., Lin, J. F., Chen, H. E., Lin, Y. C., Chou, K. Y., Hwang, T. I. S.", "Induction of autophagic death by benzyl isothiocyanate in human prostate cancer cells", "", "17:A164-A165", "620ed1fc-e700-4b0d-9ec4-98d9e1d59d1b", "", "Purpose: A number of studies support that certain food phytochemicals protect against cancer. An important group of compounds that have this property are organosulfur compounds including isothiocyanates (ITCs). Among them, benzyl isothiocyanate (BITC) has been shown to induce apoptosis in various cancer cell lines. In this study, we investigate whether BITC induces autophagy, a type-II programmed cell death, in human prostate cancer cell lines. Materials and methods: We have examined the cell death pattern induced by BITC on PC-3 and CRW22Rv1 (androgen-independent and sensitive human prostate cancer cell lines, respectively) cells survival by MTT assay. The digestion and formation of LC3-II, a marker protein involved in the formation of autophagosome during autophagic cell death, was detected by Western blot. Formation of acidic organelles was detected by acridine orange staining and LC3-II incorporation by Immunofluorescent (IF) staining. Results: Significant dose and time-dependent growth inhibition on both PC-3 and CRW22Rv1 cells was observed in BITC treatment. The cytotoxicity of BITC was greater than AITC in the same concentration. Formation of LC3-II was detectable at 7.5p.M, and increased at 20p.M after 24 hours of BITC treatment. Acidic organelles were first detectable by acridine orange staining. IF showed round-up and condensed staining of LC3-II, suggesting the formation of autophagosome in the cytoplasm during autophagic cell death. Conclusion: This is the first study showed that BITC markedly inhibit PC-3 and CRW22Rv1 cancer cell growth through autophagic cell death. This finding could potentially contribute to the beneficial effect of BITC in prostate cancer treatments.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Tsuda, T., Tokinobu, A., Yamamoto, E., Suzuki, E.", "Thyroid Cancer Detection by Ultrasound Among Residents Ages 18 Years and Younger in Fukushima, Japan: 2011 to 2014", "", "", "93d89456-8206-41a2-8995-7149983172f2", "", "BACKGROUND:: After the Great East Japan Earthquake and Tsunami in March 2011, radioactive elements were released from the Fukushima Daiichi Nuclear Power Plant. Based on prior knowledge, concern emerged about whether an increased incidence of thyroid cancer among exposed residents would occur as a result. METHODS:: After the release, Fukushima Prefecture performed ultrasound thyroid screening on all residents ages ≥18 years. The first round of screening included 298,577 examinees, and a second round began in April 2014. We analyzed the prefecture results from the first and second round up to December 31, 2014, in comparison with the Japanese annual incidence and the incidence within a reference area in Fukushima Prefecture. RESULTS:: The highest incidence rate ratio, using a latency period of 4 years, was observed in the central middle district of the prefecture compared with the Japanese annual incidence (incidence rate ratio = 50; 95% confidence interval [CI] = 25, 90). The prevalence of thyroid cancer was 605 per million examinees (95% CI = 302, 1,082) and the prevalence odds ratio compared with the reference district in Fukushima Prefecture was 2.6 (95% CI = 0.99, 7.0). In the second screening round, even under the assumption that the rest of examinees were disease free, an incidence rate ratio of 12 has already been observed (95% CI = 5.1, 23). CONCLUSIONS:: An excess of thyroid cancer has been detected by ultrasound among children and adolescents in Fukushima Prefecture within 4 years of the release, and is unlikely to be explained by a screening surge. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-

No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2012", "Vega, F. M., Colomba, A., Reymond, N., Thomas, M., Ridley, A. J.", "RhoB regulates cell migration through altered focal adhesion dynamics", "Open biology", "2(5):120076", "0abbd9c99-c6b4-4353-92dc-2377f51fcd9c", "", "The Rho GTPase RhoB has been shown to affect cell migration, but how it does this is not clear. Here we show that cells depleted of RhoB by RNAi are rounded and have defects in Rac-mediated spreading and lamellipodium extension, although they have active membrane ruffling around the periphery. Depletion of the exchange factor GEF-H1 induces a similar phenotype. RhoB-depleted cells migrate faster, but less persistently in a chemotactic gradient, and frequently round up during migration. RhoB-depleted cells have similar numbers of focal adhesions to control cells during spreading and migration, but show more diffuse and patchy contact with the substratum. They have lower levels of surface  $\beta$ 1 integrin, and  $\beta$ 1 integrin activity is reduced in actin-rich protrusions. We propose that RhoB contributes to directional cell migration by regulating  $\beta$ 1 integrin surface levels and activity, thereby stabilizing lamellipodial protrusions.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2000", "Walsh, L. P., McCormick, C., Martin, C., Stocco, D. M.", "Roundup inhibits steroidogenesis by disrupting steroidogenic acute regulatory (StAR) protein expression", "Environmental health perspectives", "108(8):769-76", "138d5821-ba60-4cad-a45a-f2822e299fd8", "", "Recent reports demonstrate that many currently used pesticides have the capacity to disrupt reproductive function in animals. Although this reproductive dysfunction is typically characterized by alterations in serum steroid hormone levels, disruptions in

spermatogenesis, and loss of fertility, the mechanisms involved in pesticide-induced infertility remain unclear. Because testicular Leydig cells play a crucial role in male reproductive function by producing testosterone, we used the mouse MA-10 Leydig tumor cell line to study the molecular events involved in pesticide-induced alterations in steroid hormone biosynthesis. We previously showed that the organochlorine insecticide lindane and the organophosphate insecticide Dimethoate directly inhibit steroidogenesis in Leydig cells by disrupting expression of the steroidogenic acute regulatory (StAR) protein. StAR protein mediates the rate-limiting and acutely regulated step in steroidogenesis, the transfer of cholesterol from the outer to the inner mitochondrial membrane where the cytochrome P450 side chain cleavage (P450<sub>scc</sub>) enzyme initiates the synthesis of all steroid hormones. In the present study, we screened eight currently used pesticide formulations for their ability to inhibit steroidogenesis, concentrating on their effects on StAR expression in MA-10 cells. In addition, we determined the effects of these compounds on the levels and activities of the P450<sub>scc</sub> enzyme (which converts cholesterol to pregnenolone) and the 3 $\beta$ -hydroxysteroid dehydrogenase (3 $\beta$ -HSD) enzyme (which converts pregnenolone to progesterone). Of the pesticides screened, only the pesticide Roundup inhibited dibutyryl [(Bu)<sub>2</sub>]cAMP-stimulated progesterone production in MA-10 cells without causing cellular toxicity. Roundup inhibited steroidogenesis by disrupting StAR protein expression, further demonstrating the susceptibility of StAR to environmental

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2002", "Watson, C. S., Campbell, C. H., Gametchu, B.", "The dynamic and elusive membrane estrogen receptor-

alpha", "Steroids", "67(6):429-37", "61d58781-ec6e-4681-827a-73d6824bcb0f", "", "Many studies have demonstrated the nuclear forms of steroid receptors and their activities, while fewer investigators have identified and described the membrane forms of these receptors. Our immuno-identification approaches for the qualitative and quantitative comparison of the membrane form of the estrogen receptor-alpha (mER alpha) to its nuclear counterpart now allow us to address questions about the comparative levels and regulation of these receptor forms. ER alpha-specific antisense oligonucleotides eliminate mER alpha expression, while only mildly reducing the nuclear ER alpha. Success of immuno-identification for the mER alpha is very sensitive to different fixation protocols, affecting cell permeability (and thus distinction from the intracellular form) and differential epitope preservation. All such identifications must be accompanied by proof of cell membrane integrity and focal plane assessments. The mER alpha expression on selected cells declines rapidly with cell passage number and cell density. Expression of mER alpha is enhanced by serum starvation and selection for specific phases of the cell cycle. The hinge region of the protein is sensitive to ligand-induced epitope masking and to antibody-induced changes in receptor-mediated responses. Responsive cells are often diluted within cell populations by loss of the membrane receptor form. The bimodality of the rapid estrogen action, with inhibitory doses between picomolar and nanomolar stimulatory concentrations, requires detailed dose-response curves. Finally, responsive cells can be lost from assays, as upon estrogen treatment they rapidly round up and leave the substrates to which they are attached. These regulatory phenomena demonstrate that levels of the membrane form of the estrogen receptor are very dynamic.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

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cortical actin network during mitosis", "American journal of physiology. Cell physiology", "305(1):C36-47", "7d0f0eea-1d48-489e-8772-8261f002a4d2", "", "Mutations in inversin cause nephronophthisis type II, an autosomal recessive form of polycystic kidney disease associated with situs inversus, dilatation, and kidney cyst formation. Since cyst formation may represent a planar polarity defect, we investigated whether inversin plays a role in cell division. In developing nephrons from inv-/- mouse embryos we observed heterogeneity of nuclear size, increased cell membrane perimeters, cells with double cilia, and increased frequency of binuclear cells. Depletion of inversin by siRNA in cultured mammalian cells leads to an increase in bi- or multinucleated cells. While spindle assembly, contractile ring formation, or furrow ingression appears normal in the absence of inversin, mitotic cell rounding and the underlying rearrangement of the cortical actin cytoskeleton are perturbed. We find that inversin loss causes extensive filopodia formation in both interphase and mitotic cells. These cells also fail to round up in metaphase. The resultant spindle positioning defects lead to asymmetric division plane formation and cell division. In a cell motility assay, fibroblasts isolated from inv-/- mouse embryos migrate at half the speed of wild-type fibroblasts. Together these data suggest that inversin is a regulator of cortical actin required for cell rounding and spindle positioning during mitosis. Furthermore, cell division defects resulting from improper spindle position and perturbed actin organization contribute to altered nephron morphogenesis in the absence of inversin.", "", "", "RefMan", "", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2000", "Williams, G. M., Kroes, R., Munro, I. C.", "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans", "Regulatory toxicology and pharmacology : RTP", "31(2 Pt 1):117-65", "a18160ed-2087-44ad-a4be-11f5ac595f38", "", "Reviews on the safety of glyphosate and Roundup herbicide that have been conducted by several regulatory agencies and scientific institutions worldwide have concluded that there is no indication of any human health concern. Nevertheless, questions regarding their safety are periodically raised. This review was undertaken to produce a current and comprehensive safety evaluation and risk assessment for humans. It includes assessments of glyphosate, its major breakdown product [aminomethylphosphonic acid (AMPA)], its Roundup formulations, and the predominant surfactant [polyethoxylated tallow amine (POEA)] used in Roundup formulations worldwide. The studies evaluated in this review included those performed for regulatory purposes as well as published research reports. The oral absorption of glyphosate and AMPA is low, and both materials are eliminated essentially unmetabolized. Dermal penetration studies with Roundup showed very low absorption. Experimental evidence has shown that neither glyphosate nor AMPA bioaccumulates in any animal tissue. No significant toxicity occurred in acute, subchronic, and chronic studies. Direct ocular exposure to the concentrated Roundup formulation can result in transient irritation, while normal spray dilutions cause, at most, only minimal effects. The genotoxicity data for glyphosate and Roundup were assessed using a weight-of-evidence approach and standard evaluation criteria. There was no convincing evidence for direct DNA damage in vitro or in vivo, and it was concluded that Roundup and its components do not pose a risk for the production of heritable/somatic mutations in humans. Multiple lifetime feeding studies have failed to demonstrate any tumorigenic potential for glyphosate. Accordingly, it was concluded that glyphosate is noncarcinogenic. Glyphosate, AMPA, and POEA were not teratogenic or developmentally toxic. There were no effects on fertility or reproductive parameters in

two multigeneration reproduction studies with glyphosate. Likewise there were no adverse effects in reproductive tissues from animals treated with glyphosate, AMPA, or POEA in chronic and/or subchronic studies. Results from standard studies with these materials also failed to show any effects indicative of endocrine modulation. Therefore, it is concluded that the use of Roundup herbicide does not result in adverse effects on development, reproduction, or endocrine systems in humans and other mammals. For purposes of risk assessment, no-observed-adverse-effect levels (NOAELs) were identified for all subchronic, chronic, developmental, and reproduction studies with glyphosate, AMPA, and POEA. Margins-of-exposure for chronic risk were calculated for each compound by dividing the lowest applicable NOAEL by worst-case estimates of chronic exposure. Acute risks were assessed by comparison of oral LD50 values to estimated maximum acute human exposure. It was concluded that, under present and expected conditions of use, Roundup herbicide does not pose a health risk to humans."

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"Unknown","Unknown","Unknown","Unknown","","","2014","Wunnapuk, K., Gobe, G., Endre, Z., Peake, P., Grice, J. E., Roberts, M. S., Buckley, N. A., Liu, X.,""Use of a glyphosate-based herbicide-induced nephrotoxicity model to investigate a panel of kidney injury biomarkers","Toxicology letters","225(1):192-200","991c65c2-5bc5-4d0f-9c67-5305dd2f6e79","","Accidental or intentional ingestion of glyphosate surfactant-based herbicides, like Roundup((R)), leads to nephrotoxicity as well as death. In this study, a panel of kidney injury biomarkers was evaluated in terms of suitability to detect acute kidney injury and dysfunction. The Roundup((R)) intoxication model involved oral administration of glyphosate to rats at dose levels of 250, 500, 1200 and 2500 mg/kg. Urinary and plasma biomarker patterns were investigated at 8, 24 and 48 h after dosing. Biomarkers were quantified by absolute concentration; by normalising to urine creatinine; and by calculating the excretion rate. The diagnostic performances of each method in predicting of acute kidney injury were compared. By Receiver Operating Characteristic (ROC) analysis of the selected biomarkers, only urinary kidney injury molecule-1 (KIM-1) best predicted histological changes at 8h (best cut-off point>0.00029 mug/ml). Plasma creatinine performed better than other biomarkers at 24 h (best cut-off point>0.21 mg/dl). Urinary KIM-1 was the best early biomarker of kidney injury in this glyphosate-induced nephrotoxicity model."

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"Unknown","Unknown","Unknown","Unknown","","","2012","Zaritsky, A., Natan, S., Ben-Jacob, E., Tsarfaty, I.,""Emergence of HGF/SF-induced coordinated cellular motility","PloS one","7(9):e44671","2ec17556-842e-4bd6-9084-2664d3ae2f2b","","Collective cell migration plays a major role in embryonic morphogenesis, tissue remodeling, wound repair and cancer invasion. Despite many decades of extensive investigations, only few analytical tools have been developed to enhance the biological understanding of this important phenomenon. Here we present a novel quantitative approach to analyze long term kinetics of bright field time-lapse wound healing. Fully-automated spatiotemporal measures and visualization of cells' motility and implicit morphology were proven to be sound, repetitive and highly informative compared to single-cell tracking analysis. We study cellular collective migration induced by tyrosine kinase-growth factor signaling (Met-Hepatocyte Growth Factor/Scatter Factor (HGF/SF)). Our quantitative approach is applied to demonstrate that collective migration of the adenocarcinoma cell lines is characterized by simple morpho-kinetics. HGF/SF induces complex morpho-kinetic coordinated collective

migration: cells at the front move faster and are more spread than those further away from the wound edge. As the wound heals, distant cells gradually accelerate and enhance spread and elongation -resembling the epithelial to mesenchymal transition (EMT), and then the cells become more spread and maintain higher velocity than cells located closer to the wound. Finally, upon wound closure, front cells halt, shrink and round up (resembling mesenchymal to epithelial transition (MET) phenotype) while distant cells undergo the same process gradually. Met inhibition experiments further validate that Met signaling dramatically alters the morpho-kinetic dynamics of the healing wound. Machine-learning classification was applied to demonstrate the generalization of our findings, revealing even subtle changes in motility patterns induced by Met-inhibition. It is concluded that activation of Met-signaling induces an elaborated model in which cells lead a coordinated increased motility along with gradual differentiation-based collective cell motility dynamics. Our quantitative phenotypes may guide future investigation on the molecular and cellular mechanisms of tyrosine kinase-induced coordinate cell motility and morphogenesis in

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"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2004", "Zhao, S., Yang, Y. N., Song, J. G.", "Ceramide induces caspase-dependent and -independent apoptosis in A-431 cells", "Journal of cellular physiology", "199(1):47-56", "67d9fe5a-568c-4571-a0a3-839e7bcd01eb", "", "We investigated the ceramide-induced apoptosis and potential mechanism in A-431 cells. Ceramide treatment causes the round up and the death of A-431 cells that is associated with p38 activation and can be observed in 10 h. Short-time ceramide treatment-induced cell death is not associated with the typical apoptotic phenotypes, such as the translocation of phosphatidylserine (PS) from inner layer to outer layer of the plasma membrane, loss of mitochondrial membrane potential, DNA fragmentation, caspase activation, and PARP or PKC-delta degradation. SB202190, a specific inhibitor of p38 mitogen-activated protein (MAP) kinase, but not caspase inhibitor, blocks the cell death induced by short-time ceramide treatment (within 12 h). Whereas neither inhibition of p38 MAP kinase nor inhibition of caspases blocks cell death induced by prolonged ceramide treatment. Moreover, incubation of cells with ceramide for a long time (over 12 h) results in the reduction of proportion of S phase accompanied with typical apoptotic cell death phenotypes that are different from the cell death induced by short-time ceramide treatment. Our data demonstrated that ceramide-induced apoptotic cell death involves both caspase-dependent and caspase-independent signaling pathways. The caspase-independent cell death that occurred in relatively early stage of ceramide treatment is mediated via p38 MAP kinase, which can progress into a stage that is associated with changes of cell cycle events and involves both caspase-dependent and -independent

mechanisms.", "", "", "RefMan", "", "", "", "", "", "", "", "", ""

"Unknown", "Unknown", "Unknown", "Unknown", "", "", "2015", "Zlotek-Zlotkiewicz, E., Monnier, S., Cappello, G., Le Berre, M., Piel, M.", "Optical volume and mass measurements show that mammalian cells swell during mitosis", "The Journal of cell biology", "211(4):765-74", "641c70e8-5da4-4c5d-8b45-8a2a1e04ad12", "", "The extent, mechanism, and function of cell volume changes during specific cellular events, such as cell migration and cell division, have been poorly studied, mostly because of a lack of adequate techniques. Here we unambiguously report that a large range of mammalian cell types display a significant increase in volume during mitosis (up to 30%). We further show that this increase in volume is tightly linked to the mitotic state of the cell and not to its

spread or rounded shape and is independent of the presence of an intact actomyosin cortex. Importantly, this volume increase is not accompanied by an increase in dry mass and thus corresponds to a decrease in cell density. This mitotic swelling might have important consequences for mitotic progression: it might contribute to produce strong pushing forces, allowing mitotic cells to round up; it might also, by lowering cytoplasmic density, contribute to the large change of physicochemical properties observed in mitotic cells."

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"Unknown","Unknown","Unknown","Unknown","","","2013","Zulet, A., Gil-Monreal, M., Villamor, J. G., Zabalza, A., van der Hoorn, R. A., Royuela, M.,"Proteolytic pathways induced by herbicides that inhibit amino acid biosynthesis","PloS one","8(9):e73847","78f5c60f-cd24-4657-a63c-c745e551902b","","BACKGROUND: The herbicides glyphosate (Gly) and imazamox (Imx) inhibit the biosynthesis of aromatic and branched-chain amino acids, respectively. Although these herbicides inhibit different pathways, they have been reported to show several common physiological effects in their modes of action, such as increasing free amino acid contents and decreasing soluble protein contents. To investigate proteolytic activities upon treatment with Gly and Imx, pea plants grown in hydroponic culture were treated with Imx or Gly, and the proteolytic profile of the roots was evaluated through fluorogenic kinetic assays and activity-based protein profiling. RESULTS: Several common changes in proteolytic activity were detected following Gly and Imx treatment. Both herbicides induced the ubiquitin-26 S proteasome system and papain-like cysteine proteases. In contrast, the activities of vacuolar processing enzymes, cysteine proteases and metacaspase 9 were reduced following treatment with both herbicides. Moreover, the activities of several putative serine protease were similarly increased or decreased following treatment with both herbicides. In contrast, an increase in YVADase activity was observed under Imx treatment versus a decrease under Gly treatment. CONCLUSION: These results suggest that several proteolytic pathways are responsible for protein degradation upon herbicide treatment, although the specific role of each proteolytic activity remains to be determined."

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